# Antibiotic Policies: Fighting Resistance

# Antibiotic Policies: Fighting Resistance

Edited by

Ian M Gould
*Aberdeen Royal Infirmary*
*Foresterhill, Aberdeen*
*Australia*

and

Jos WM van der Meer
*Radboud University*
*Nijmegen Medical Centre*
*Nijmegen, The Netherlands*

Springer

Ian M Gould
Department of Medical Microbiology
Aberdeen Royal Infirmary
Foresterhill, Aberdeen
Australia

Jos WM van der Meer
Department of General Internal Medicine &
Nijmegen University Centre for
Infectious Diseases
Radboud University
Nijmegen Medical Centre
Nijmegen, The Netherlands

ISBN-13: 978-0-387-70840-9 e-ISBN-13: 978-0-387-70840-9

Library of Congress Control Number: 2007928413



Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

springer.com

# Contents

# Contributors

**Duygu Yazgan Aksoy**
Department of Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey

**Marc J. M. Bonten**
Department of Internal Medicine and Infectious Diseases, University Medical Centre, Utrecht, The Netherlands

**Michael A. Borg**
ARMed Project, St. Luke's Hospital, Guardamangia, Malta

**Emilio Bouza**
Department of Clinical Microbiology and Infectious Diseases, Hospital General, Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

**Roberto Cauda**
Department of Infectious Disease, Gemelli Hospital, Università Cattolica del Sacro Cuore Medical School, Rome, Italy

**Oana Ciofu**
Institute of Medical Microbiology and Immunology, University of Copenhagen, Copenhagen, Denmark

**Fiona Cooke**
MRC Clinical Research Training Fellow, Imperial College London, London, United Kingdom, The Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom

**Stephanie J. Dancer**
Department of Microbiolog, Southern General Hospital, Glasgow, Scotland

**Bram M. W. Diederen**
Laboratory of Medical Microbiology and Immunology, St. Elisabeth Hospital, Tilburg, The Netherlands

**Ian M. Gould**
Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Australia

**Richard P. T. M. Grol**
Department of General Practice, Centre for Quality of Care Research, Radboud University, Nijmegen, The Netherlands

**Stephan Harbarth**
Infection Control Program, University Hospitals of Geneva, Geneva, Switzerland

**Niels Høiby**
Institute of Medical Microbiology and Immunology, University of Copenhagen, Department of Clinical Microbiology and Danish Cystic Fibrosis Center, Rigshospitalet, Copenhagen, Denmark

**Alison Holmes**
Department of Infectious Diseases, Imperial College London and Hammersmith Hospitals NHS Trust, London, United Kingdom

**Jan A. J. W. Kluytmans**
Laboratory of Microbiology and Infection Control, Amphia Hospital, Breda, The Netherlands

**Leonard Leibovici**
Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tiqwa, Israel, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel

**Dominique L. Monnet**
National Center for Antimicrobials and Infection Control, Statens Serum Institut, Copenhagen, Denmark

**Patricia Muñoz**
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

**Jan Jelrik Oosterheert**
Department of Internal Medicine and Infectious Diseases, University Medical Centre, Utrecht, The Netherlands

**Amy Pakyz**
School of Pharmacy, Department of Pharmacy, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, VA, USA

**Mical Paul**
Department of Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tiqwa, Israel, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Tel Aviv, Israel

**Ron Polk**
School of Pharmacy, Department of Pharmacy, School of Medicine, Department of Internal Medicine, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, VA, USA

**R. Andrew Seaton**
Infectious Diseases Unit, Brownlee Centre, Gartnavel General Hospital, Glasgow, Scotland

**E. Tacconelli**
Department of Infectious Diseases, Catholic University, Rome, Italy, Division of Infectious Diseases, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

**Mine Durusu Tanriover**
Department of Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey

**María V. Torres**
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

**Serhat Unal**
Department of Medicine, Section of Infectious Diseases, Hacettepe University Faculty of Medicine, Ankara, Turkey

**Jos W. M. van der Meer**
Department of General Internal Medicine & Nijmegen University Centre for Infectious Diseases, Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands

**Giorgio Zanetti**
Division of Hospital Preventive Medicine and Service of Infectious Diseases, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

# Foreword

In 1971, I started a fellowship in infectious diseases and medical microbiology at the Channing Laboratory of the Harvard Medical Service at Boston City Hospital. My mentor, Dr. Maxwell Finland, had encouraged me to return there from the Center for Disease Control (as CDC was known then), where I had studied infectious diseases epidemiology and hospital-associated infection epidemiology, with the idea that we would review the demographic patterns of bacteremia and several other infections during Dr. Finland's long tenure at the hospital. We did so, but I was surprised to find that he also invited me to help with the assessment of the success or failure of the programs to control antimicrobial use that he and colleagues had put into place at the hospital over several years. The paper describing that review finally was published in 1974, after a long and tortuous process of review at several journals. Several reviewers felt that such attempts to improve use amounted to interference with the patient's physician to do what was best. Others felt that such programs focused incorrectly on a subject other than treating the current patient.

Fortunately, today, it is clear that antimicrobial resistance results in major part, but not entirely, from the ways that we use antimicrobial agents, and that the overall interests of patients in general, as well as those of society, are well served by efforts to use these drugs as well as possible. Many nations have established rubrics for this, and guidelines on such stewardship now have been published by professional societies such as the Infectious Diseases Society of America. The principle, then, now is well-established. The problem remains, however, as to the best way to accomplish this lofty goal. In the three decades that I have been involved in looking at this problem, two important guides stand out:

1. *All attempts to deal with resistance must be local*. The problems of multidrug-resistant bacteria facing a hospital in Manchester, U.K. may be quite different than those of a hospital in Manchester, New Hampshire, USA (and, in fact, may be quite different than those of a hospital just down the street from the one in Manchester, U.K.). Knowing local patterns of resistance is crucial to selection of the proper plans to improve antimicrobial use in each local setting.

2. *One size does not fit all*. No single dictum or nostrum can be devised that will deal with the resistance patterns, resources, and other risk determinants for resistance in every healthcare institution. Rigid national guidelines that work in all regions do not exist. Rigid regional guidelines that work in all local areas do not exist. Rigid municipal guidelines that work in all healthcare institutions and settings in the city do not exist. Instead, efforts should focus as suggested by the recent guidelines on dealing with multidrug resistant organisms in U.S. healthcare settings from the Centers for Disease Control and Prevention (as CDC is known now). These recommendations stress that each institution must customize its own approach to improving drug use, to controlling transmission of resistant organisms within the institution, and to conducting the surveillance needed to guide these efforts.

This volume, edited by Ian Gould and Jos van der Meer, appeals to me because it recognizes these two main principles in its advice to the worker in this field. The chapters come from many experts in many different countries who work in many different settings. They focus on practical issues of improving antimicrobial use, and consider several tools, old and new, useful in this quest. The authors speak from experience, as they work in their daily practice on the very issues that they address. All these features, plus the guiding hands of Drs. Gould and van der Meer, who have helped us understand these matters for many years, suggest that the reader will find this new compendium a valuable and practical resource.

The area of improving antimicrobial use is one that will continue to vex us for many years. However, the goal of such efforts makes the journey worth the fret. Books such as these make the journey easier.

John McGowan

# Preface

Possibly the main need for antibiotic policies is to control resistance. There is a large body of published literature on the ability of antibiotic policies to do this but robust evidence is harder to find. Often implementation is difficult, benefits are only short term or the situation is too complex in the first place for there to be any significant changes.

This volume (and the previous one in the series) deals with these issues and also looks at many of the crucial issues of resistance in a clinical context, with an emphasis on MRSA; surely the greatest challenge to our antibiotic and infection control policies that modern healthcare systems have ever seen. Other fascinating chapters explore the psychology of prescribing, modern management techniques as an adjunct to antibiotic policies, and the less obvious downsides of antibiotic use. Lastly, several chapters from authors living in Mediterranean countries give a perspective from an area of the world with some of the greatest problems in antibiotic use and resistance.

It is again a great pleasure for us to have been able to assemble such a distinguished group of international scientists to write definitive texts on these pressing problems.

# Chapter 1
# Consequences of Antimicrobial Chemotherapy: Overgrowth, Resistance, and Virulence

Stephanie J. Dancer

## Summary

The right antibiotic, given at the right time and in the correct dose, can cure infection and save lives. Unfortunately, these drugs cause adverse effects, which sometimes make things worse. These may be due to resistant organisms that overgrow in response to a course of antibiotics, or they may be due to the fact that the original pathogen was not eradicated and continues to cause a problem. It is even possible that the original pathogen actually becomes more virulent following exposure to antibiotics. This article reviews the evidence that getting it wrong regarding antibiotic therapy creates more problems for individual patients as well as encouraging antibiotic resistance for future patients.

## Introduction

Every time a patient takes an antibiotic, it inhibits or kills a whole range of bacteria. This creates space on mucosal and other surfaces for other organisms to proliferate (Van der Waaij 1987). These survivors may be naturally resistant to the antibiotic ingested, or they may have acquired resistance during therapy. Sometimes the patient was already colonized with resistant organisms before treatment had even begun. Perhaps the best-known survivor is *Candida albicans*, a yeast that overgrows in response to almost any course of antibiotics (Wey et al. 1989). Thrush infections can be a real problem for community-based patients as well as hospital patients, and can easily kill patients in the intensive care unit. Other naturally occurring commensals include the spore-forming *Clostridium difficile* in the human gut, which will overgrow following a course of broad-spectrum antibiotics and precipitate antibiotic-associated diarrhoea (Farrell and LaMont 2000, Dancer 2001). This is a debilitating infection for hospital patients, already compromised by various preexisting conditions. New strains have emerged recently that are far more virulent than usual, and these are associated with increased morbidity and mortality (Pepin et al. 2004). In the intensive care unit, the powerful carbapenem antibiotics

select for naturally carbapenem-resistant *Stenotrophomonas maltophilia*, which causes a similar spectrum of infections in ventilated patients as *Pseudomonas aeruginosa*; one major difference, however, is that *S. maltophilia* is multiply resistant to antibiotics and is thus more difficult to treat than pseudomonas (Sanyal and Mokaddas 1999).

These organisms are naturally resistant to the drugs used but some organisms can acquire resistance to whichever antibiotic is given during the course of therapy. Overgrowth occurs following huge expansion of one or more bacterial cells that had the capacity for resistance in the original population. This capacity for resistance might even have been provided by neighboring commensals, by transferring various resistance elements to the population under threat. It is well known that bacteria can share genetic information with members of their own, and other, species. Their promiscuity even extends to different genera, so that genes can be transferred between Gram-negative and Gram-positive organisms. Examples of resistance evolving *in vivo* include methicillin-resistant *Staphylococcus aureus* (MRSA) following treatment with any β-lactam antibiotic, ciprofloxacin resistance in *P.aeruginosa* after quinolone exposure, fusidic acid and fucidin-resistant *S. aureus*, and the appearance of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLs) after third-generation cephalosporins (Muller et al. 2003, Dostal, Seale and Yan 1992, Mason, Howard and Magee 2003, Pechere 1989). Thus, antibiotics select for organisms that are naturally resistant and encourage resistance in those that are not.

Managing an infection caused by a resistant organism is difficult even if the causative organism is isolated and identified. If it remains undetected, antibiotics simply make things worse (Dancer 2004). Even an appropriate antibiotic may do more harm than good, if it is given for too short a time, or in too low a dose (Klugman 2003). These drugs eradicate susceptible commensal competitors and thus create more space and access to nutrients for the pathogen. When an organism proliferates, the signs and symptoms of infection become more obvious; this is assumed to be due to the sheer quantity of bacterial cells provoking the usual inflammatory reaction, but pathogens are able to invoke something more by which to advance infection. Having colonized a site and established themselves, they can switch on various virulence determinants in order to facilitate invasion and thus survival. Prominent pathogens will exhibit virulence whether encouraged by inappropriate antibiotics or not, but there is evidence to suggest that the wrong antibiotic will enhance and even accelerate virulence of a potential pathogen *in vivo*, including organisms that are generally regarded only as commensals. This can sometimes make the difference between a patient surviving an infection or not, since the effects of serious sepsis can occasionally be too far advanced to manage successfully (Harbarth et al., 2003).

Below follows a review of some of the virulence determinants of pathogens, and how they might be affected by antibiotic therapy.

## Aspects of Virulence: Quorum Sensing

Treatment with antibiotics results in rapid proliferation of organisms, which are then subject to a chemical signaling mechanism called *quorum sensing* (Finch et al. 1998). This mechanism allows bacteria to detect the density of their own species and alter their genetic expression in order to take advantage of this knowledge. Each bacterium's behavior is affected by the presence of its own kind and, more specifically, by a predetermined density of their fellow species to make a genetic switch worthwhile (Donabedian 2003). This switch confers a survival advantage to the bacteria, in that the original requirement for colonization is superseded by a requirement for deeper penetration into the tissues once the number of cells in the colony reaches a set level. Uncontrolled proliferation of a species would soon result in compromise, since there is a limit on space and nutrients at a single bodily site. Further perpetuation of the species, just like an invading army, requires access to other sites in search of essential stores. The need to express genes coding for adhesion becomes obsolete; now, the bacterium must repress such genes and instead release those that would facilitate various mechanisms for spread into the tissues and particularly into the systemic circulation. Access to the bloodstream, causing bacteremia or even septicemia for the patient, is an excellent way of initiating a bacterial search party to find new and fertile pastures.

There are several well-known pathogens that utilize quorum sensing in various different ways in order to exert their effects: *Streptococcus pneumoniae, P.aeruginosa*, and *S. aureus* are three examples (Donabedian 2003). At a certain bacterial density *S. pneumoniae* is able to incorporate DNA from other bacteria. This ability to accept exogenous DNA sequences allows the pneumococcus to acquire genes necessary for resistance to penicillin (Morrison 1997). *P.aeruginosa* has at least two quorum sensing systems, which interact with each other (Gabello and Iglewski 1991, Hingley et al. 1986). The net effect is that at a certain density, *P.aeruginosa* switches on genes that encode several extracellular virulence factors. These include alkaline protease, toxin A and elastases, and a hemolysin thought to be a virulence factor by virtue of its ciliostatic effect on respiratory cilia. The two quorum sensing systems are linked, in that when the auto-inducer molecule belonging to one system binds to the protein responsible for enhancing the transcription of virulence factors, another gene is activated that synthesizes the second quorum-sensing molecule (Donabedian 2003).

The second system ultimately results in a number of adaptations, including biofilm formation. The interplay between these systems, and indeed, a possible third, is complex and not yet fully elucidated. It is possible that there are advantages from such a complex system regarding different density configurations, such as found in a biofilm as opposed to an abscess. There may be as yet many more undiscovered quorum-sensing molecules, some of which may even be able to communicate bacterial density across species barriers.

Quorum-sensing mechanisms in *S. aureus* differ from those already described but achieve similar objectives (Ji, Beavis and Novick 1995). Many staphylococcal virulence factors are regulated by the *agr* group of genes, which allow the transcription

of genes responsible for encoding a variety of toxins. It is conceivable that staphylococci originally concentrate their genetic expression on adherence at a primary site before quorum-sensing molecules signal that the required growth density has been achieved. Thereafter, a genetic switch is triggered in order to activate the *agr* locus and thus secretion of known virulence determinants such as α-toxin, β-toxin, and δ-toxin (Recse et al. 1986).

There is evidence for quorum-sensing systems in many other pathogens, including *Escherichia coli, Enterococcus faecalis, Helicobacter pylori, Candida albicans, Vibrio* spp., and *Salmonella typhimurium* (Donabedian 2003). Some utilize similar systems; others actively metabolize signaling molecules from other species in order to disrupt the quorum-sensing process belonging to potential competitors. Inappropriate or insufficient antimicrobial chemotherapy, by removing susceptible commensals, encourages the growth of a pathogen and thereby accelerates the quorum-sensing process, turning a relatively benign visitor into a virulent invader. The system does, however, offer an additional target for potential therapy in the future, in that natural and artificial peptide inhibitors of the quorum sensing response have already been evaluated *in vitro* (Gorske and Blackwell 2006). Biostable peptide blockers might not eradicate the targeted pathogen but would allow more time for conventional antibiotics to exert their effect before the virulence switch is activated.

## Aspects of Virulence: Toxin Production

It has been known for some time that antibiotics are capable of modifying the metabolic processes of bacteria when they are incorporated into culture media at subinhibitory concentrations (Lorian and Gemmell 1991). This includes the expression of virulence-associated genes in pathogens. Not all antibiotics exert the same effect, however, since there appears to be a differential effect dependent on the pathogen and antibiotic pair under investigation (Worlitzsch et al. 2001, Drummond, Smith and Poxton 2003). Since some of the products of virulence-associated genes can be measured, it is possible to rank individual antibiotics in order of their effect on the production of toxins and other virulence determinants.

*S. aureus* produces many toxins, one of which, the staphylococcal α-toxin, is a major virulence determinant encoded by the *hla* gene (Bhakdi and Tranum-Jensen 1991). It has been shown that growing *S. aureus* in the presence of the β-lactam antibiotic, nafcillin, induces α-toxin expression and increases the lethal activity of broth filtrates in rats (Kernodle et al. 1995). These findings led to the speculation that β-lactam therapy might enhance the virulence of some *S. aureus* strains, in turn worsening the symptoms of serious staphylococcal infection. Therefore, the effects of other antibiotics have been tested by measuring the induction of *hla* expression after exposure to different strains of *S. aureus* (Ohlsen et al. 1998). There was a strong induction of *hla* expression by subinhibitory concentrations of several β-lactam antibiotics, including some cephalosporins and imipenem. Fluoroquinolones slightly stimulated expression,

glycopeptide antibiotics had no effect, and erythromycin and aminoglycosides reduced expression. Clindamycin almost completely inhibited the expression of α-toxin. Furthermore, methicillin-induced *hla* expression appears to be a common phenomenon of α-toxin-producing strains of both methicillin-susceptible and methicillin-resistant *S. aureus*. Some MRSA strains produced up to 30-fold more α-toxin in the presence of 10 μg of methicillin per milliliter than in its absence (Ohlsen et al. 1998).

Another toxin associated with *S. aureus* is the toxic shock syndrome toxin (TSST), originally described in conjunction with tampon use in adult women. There is little evidence linking inappropriate or inadequate antibiotics with increased production of TSST but it is of interest that in a recent report of two pediatric cases of toxic shock syndrome, both received cephalosporin antibiotics before their rapid deterioration forced a change to more effective therapy (Taylor, Riordan and Graham 2006). There are several reports that prior antibiotics may encourage nonmenstrual toxic shock syndrome, as well as recurrent episodes of the syndrome (Kain, Schulzer and Chow 1993, Andrews et al. 2001). Yet more staphylococcal toxins, the enterotoxins, have been associated with postoperative enteritis caused by MRSA; fatal staphylococcal enteritis following antibiotic therapy was well described during the 1960s (Kodama et al. 1997, Altemeier, Hummel and Hill 1963).

Certain antibiotics obviously have the capacity for inducing the release of exotoxins, which enhance *S. aureus*-related toxic syndromes. Others appear to actively inhibit toxin production and thus attenuate virulence (Herbert, Barry and Novick 2001, Koszczol et al. 2006). In addition, these agents downregulate the proinflammatory host response as well. The streptogramin antibiotic, quinupristin/dalfopristin, and the oxazolidinone, linezolid, dose-dependently reduce the induction of TNF-releasing activity by *S. aureus* toward host cells (Bernardo et al. 2004, Koszczol et al. 2006).

*P.aeruginosa* also produces toxins, including endotoxin and exotoxin A. Both of these promote the release of cytokines in the pathogenesis of septic shock. Exposure to concentrations of carbapenem antibiotics below the minimal inhibitory concentration (MIC) induces the formation of filamentous cells rather than cell death (Horii et al. 2005). This is associated with increased exotoxin A production and/or greater release of endotoxin and infers that blood concentrations of carbapenems should be kept above the MIC during the treatment of *P.aeruginosa* bacteremias (Horii et al. 2005). It has been known for some time that antibiotics that affect the bacterial cell wall increase the release of endotoxin by destroying bacterial integrity; this may tip a patient into septic shock, even if the antibiotic administered is entirely appropriate for the causative pathogen (Hurley 1992).

A final example is a recent study on the effect of preexposure antibiotics on the production of the cytolethal-distending toxin (CDT) by *Campylobacter jejuni* (Ismaeel et al. 2005). There appears to be an association between preexposure to sub-MIC levels of ciprofloxacin and erythromycin and increased CDT production, which could potentiate CDT activity. The authors recommend that these antibiotics

should only be used in the treatment of campylobacter enteritis when strongly indicated, along with careful monitoring of patients (Ismaeel et al. 2005).

## Aspects of Virulence: Horizontal Transfer of Virulence and Resistance Genes

Bacterial DNA damage occurs when bacteria are subjected to unfavorable environmental conditions. The global response to such damage is called the SOS system, and its function is to upregulate genes involved in DNA repair and cell survival. It is well known that exposure to antibiotics will initiate the SOS response but it has only recently been shown that the response itself is capable of generating the horizontal transfer of mobile genetic elements, such as plasmids, bacteriophages, pathogenicity islands, transposons, and various insertion sequences (Hastings, Rosenberg and Slack 2004). These elements play a crucial role in spreading antibiotic resistance and virulence genes among bacterial populations. Exposure to ciprofloxacin, for example, will induce the SOS response in *Vibrio cholerae*, which then promotes the horizontal dissemination of antibiotic resistance genes via an integrating conjugative element (ICE) (Beaber, Hochhut and Waldor 2004). This element encodes genes that confer resistance to chloramphenicol, sulfamethoxazole, trimethoprim, and streptomycin, and appears to have penetrated most clinical isolates of *V. cholerae* from Asia within a decade. Thus, exposure to one antibiotic specifically promotes resistance not only to the agent used but to other antibiotics as well (Beaber, Hochhut and Waldor 2004).

β-Lactam antibiotics such as penicillin, ampicillin, cloxacillin, and ceftriaxone, induce the SOS response in *S. aureus*; this results in promotion of replication and high-frequency horizontal transfer of pathogenicity island-encoded virulence factors (Maiques et al. 2006). These pathogenicity islands carry genes for virulence determinants such as TSST, other superantigenic toxins, and biofilm promoters. Fluoroquinolones and trimethoprim have also been implicated in similar SOS induction in staphylococci (Goerke, Koller and Wolz 2006). In addition, fluoroquinolones induce an SOS response in *E. coli*, which results in horizontal transfer of bacteriophages encoding a Shiga-like toxin (Zhang et al. 2000).

It appears that nonlethal use of many antibiotics can induce the SOS response and potentially enhance the transmission not only of resistance, but of virulence factors as well. Since MRSA continues to increase in hospitals, there is concern that heterogeneous populations of *S. aureus* will serve as a reservoir of virulence genes awaiting transfer to their methicillin-resistant counterparts.

## Aspects of Virulence: Bacterial Adhesion

Bacterial adhesion plays an important role in colonization and infection. *S. aureus*, for example, adheres to plasma proteins such as fibrinogen and fibronectin, which coat implanted biomaterials such as indwelling catheters

and orthopedic devices during the early stages of infection. It has been shown that subinhibitory concentrations of antibiotics can affect staphylococcal binding to fibrinogen and collagen (Proctor, Olbrantz and Mosher 1983, Butcher et al. 1994).

Exposure of highly fluoroquinolone-resistant *S. aureus* to subinhibitory levels of ciprofloxacin significantly increases the expression of fibronectin adhesins. This leads to increased attachment of the bacterial cells to immobilized fibronectin in an *in vitro* model (Bisognano et al. 1997). Increased adhesion also occurs with other strains of staphylococci, including MRSA and methicillin-susceptible *S. aureus*. Indeed, staphylococcal expression of surface adhesins is altered following the acquisition of the methicillin resistance element *mecA* (Vaudaux et al. 1998). It is tempting to hypothesize that this antibiotic-promoted increase in adhesion might contribute towards the emergence of staphylococci expressing increased levels of antibiotic resistance. Certainly, there are a number of clinical and laboratory-based studies that suggest an association between ciprofloxacin consumption and acquisition of MRSA (Weber et al. 2003, Venezia et al. 2001, LeBlanc et al. 2006).

The glycopeptide antibiotics, vancomycin and teicoplanin, are regarded as the drugs of choice for MRSA. Resistance to these agents has already been described, along with the possibility that such resistance is associated with enhanced virulence. Some strains of vancomycin-intermediate *S. aureus* (VISA) can adhere more readily to artificial surfaces than their MRSA progenitors. There is also a rise in vancomycin minimum inhibitory concentrations in staphylococcal strains from biofilms (Williams et al. 1997). Furthermore, a teicoplanin-resistant derivative of MRSA demonstrated higher levels of fibronectin-mediated adhesion and binding proteins in a rat model of chronic foreign-body MRSA infection (Renzoni et al. 2004). The emergence of glycopeptide resistance, therefore, seems to be linked to changes in the expression and regulation of some major virulence genes in staphylococci.

## Aspects of Virulence: Pathogen Persistence

Some pathogens not only infect, but survive within, various types of host cells, including both phagocytes and nonphagocytic cells (Almeida et al. 1996, Seral et al. 2005). This ability to persist within host cells plays an important role in pathogenesis and dictates a need for antibiotics with intracellular activity.

Even though proven to be effective against *S. aureus in vitro*, certain antibiotics may not necessarily protect infected host cells from *S. aureus*-mediated cell death (Krut, Sommer and Kronke 2004). These include oxacillin, gentamicin, ciprofloxacin, trimethoprim/sulfamethoxazole, and vancomycin. Linezolid, rifampicin, clindamycin, and erythromycin suppress the cytotoxic action of *S. aureus* but most of these will only do so for as long as the antibiotic pressure is maintained. Except for rifampicin, intracellular *S. aureus* will regain its cytotoxic activity and kill the host cells following withdrawal of antibiotics. Linezolid and clindamycin can even induce a state of intracellular persistence of viable *S. aureus*.

Thus, antibiotics commonly used in the management of *S. aureus* infections may encourage invasive intracellular strains, which may play an important role in the persistence and recurrence of infection (Krut, Sommer and Kronke 2004).

## *Pathogen Persistence: Small-Colony Variants*

Long-term intracellular persistence of small colony variants of *S. aureus* has been described in association with chronic osteomyelitis, cystic fibrosis, prosthetic joint and skin infections (Sendi et al. 2006). These staphylococcal variants are able to persist under antibiotic pressure *in vivo* (Brouillette et al. 2004). A recent report even suggests that repeated treatment failures with standard antibiotic protocols might be linked with the emergence of *S. aureus* small-colony variants (Sendi et al. 2006). Exposure to different classes of antibiotics frequently contributes to the selection of these variants both *in vitro* and *in vivo*, and they are undoubtedly difficult to diagnose and difficult to treat (Vaudaux et al. 2006). They may also be found in association with biofilms, an interacting conglomeration of organisms attached to both naturally occurring and synthetic surfaces (Lindsay and von Holy 2006). Biofilms serve as protective niches for pathogens within a host or as a means of survival in the environment. They afford an opportunity for persistence and contribute toward pathogenesis in clinical settings.

## *Pathogen Persistence: Biofilms*

It is known that bacteria in biofilms are more resistant to treatment with antimicrobial agents than the corresponding free-living or planktonic cells (Donlan 2002). Drug-resistant *E. coli* biofims have been shown to exhibit β-lactamase activity, enhancing resistance to antibiotics such as imipenem and cefoxitin (He, Li and Li 2001). Small-colony variants of staphylococci within biofilms may be highly resistant to the bactericidal action of oxacillin or vancomycin (Chuard et al. 1997). It appears that a fraction of cells within a biofilm population will always exhibit a resistant phenotype (Meyer 2003); these bacteria are often termed *persister cells* (Keren et al. 2004). Studies have suggested that persisters are neither defective cells nor cells created in response to antibiotics, but are rather specialized survivor cells. Keren et al. (2004) showed that tolerance of *E. coli* to ampicillin and ofloxacin is due to persister cells.

Antibiotic susceptibility of planktonic bacteria and resistance of corresponding biofilm cells is thus a well-established phenomenon (Tenke et al. 2006). In most cases, treatment with antibiotics slows down biofilm progression by eliminating planktonic cells and interfering with biofilm metabolism. However, neither the biofilm nor the infection is eliminated effectively, and there is growing concern about the cross-resistance exhibited by antibiotic-resistant strains to other antimicrobial agents, including disinfectants (Langsrud et al. 2003, Lundén et al. 2003). Strains of *S. aureus*, which harbor plasmids coding for resistance to penicillin, also exhibit resistance to quaternary-ammonium-chloride-containing disinfectants (Langsrud et al. 2003).

There remains a challenge in elucidating the factors that make the biofilm phenotype so different from the planktonic phenotype. Perhaps one of the most important of these is the observed resistance or tolerance to antimicrobial agents (Donlan 2002).

## Aspects of Virulence: Antibiotic Resistance

There are numerous miscellaneous reports linking antibiotic resistance with a worse clinical outcome, although it must be borne in mind that increased morbidity and mortality due to infections caused by resistant organisms may only be due to the fact that they are more difficult to manage, and not necessarily because they are more virulent (Dancer 2004). Here are a few examples. Antimicrobial-resistant nontyphoidal salmonella is associated with excess bloodstream infections and hospitalizations than patients with pan-susceptible infection (Varma et al. 2005). Another food-poisoning organism, campylobacter, causes prolonged diarrhea if it is resistant to ciprofloxacin (Nelson et al. 2004). Quinolones are commonly prescribed for the treatment of campylobacteriosis in adults and usually reduce the duration of diarrhea associated with campylobacter infection. In a multivariable analysis-of-variance model, however, patients with ciprofloxacin-resistant infection had a longer mean duration of diarrhea than patients with ciprofloxacin-susceptible organisms. This effect was independent of foreign travel and consistent across a variety of analytical approaches (Nelson et al. 2004).

MRSA isolates obtained after clinical failure of vancomycin demonstrate physiological changes when compared with the original parent strain (Sakoulas et al. 2006). Analysis of the virulence regulatory group of *agr* genes from the initial bloodstream isolate showed little δ-hemolysin activity. After 9 months of vancomycin and a switch to linezolid, however, δ-hemolysin expression increased noticeably. There was also a decrease in autolysis, reduced killing by vancomycin *in vivo*, and increased biofilm formation in isolates obtained after prolonged exposure to vancomycin (Sakoulas et al. 2006). It has already been suggested that there is a link between pathogenicity and vancomycin tolerance in MRSA, since the discovery that the *agr* group of genes are implicated in the expression of penicillin-binding proteins that help establish the VISA phenotype (Schrader-Fischer and Berger-Bachi 2001).

Staphylococcal resistance contributes toward the pathogenesis of wound infections. Resistant subpopulations of staphylococci, particularly those producing β-lactamase, may account for a significant proportion of apparent prophylaxis failures. This may be due to the fact that a popular choice for antibiotic prophylaxis includes the cephalosporins, which are ineffective against MRSA as well as encouraging β-lactamase-producing borderline oxacillin-susceptible *S. aureus* (Dancer 2001, Kernodle et al. 1998). It may be relevant to note that of four pediatric deaths attributed to community-acquired MRSA, all four had received prior therapy with cephalosporins on admission to hospital (Anon. 1999). Two other children with MRSA infections required surgical management following

failed treatment with oral cephalosporins (Feder 2000). The authors warn of the need to consider MRSA as a potential cause of infection in community-based patients with no obvious risk factors, including previous hospitalization (Feder 2000).

## Conclusion

Antibiotics were a remarkable discovery and along with immunization, have revolutionized the management of infection over the last half-century. Resistance to these biological agents was inevitable and now erodes the quality and provision of healthcare at all levels. In addition, evidence is accumulating that inappropriate or inadequate antimicrobial therapy not only fails to eradicate the pathogen but also encourages resistance and even virulence. Getting it wrong regarding the empirical choice of an agent may kill a vulnerable patient; at best, the patient fails to respond, whilst the organism is given time to evolve its defense mechanisms (Kollef 2003).

Many authors, antimicrobial policies and guidelines have already called for prudence in antimicrobial prescribing, better diagnosis of infection, quicker identification of pathogens, more education for prescribers, and a constant awareness of the long-term effects of antimicrobial consumption for both patients and the environment (Kollef 2003, Dancer 2004, Shramm et al. 2006). Unfortunately, the reality is probably that nothing will change until we reach the stage where we consistently fail to find any drug whatsoever with which to treat our patients. There is a constant onslaught of antibiotic abuse, from over-the-counter antimicrobials and fake drug trafficking to antibiotic-impregnated consumables. Patients themselves don't even finish the course of drugs they are told to take. Inappropriate prescribing, for both human and nonhuman use, will continue to erode any attempts at control across the world.

It is not impossible that in the future we might experience a global pandemic of some multiply resistant pathogen that seeks to rival the postulated impact of avian influenza. Indeed the impact of any strain of pandemic influenza would be significantly accentuated by MRSA. Events such as this would put antimicrobial resistance firmly on the political agenda and help prioritize the research required for finding another way of treating infection.

Antimicrobial resistance is a wake-up call for all prescribers; take heed and be responsible for what you do. A concerted effort to minimize inappropriate prescribing would prolong the time we need to discover a future strategy for treating infection.

*Acknowledgments*. Thanks are due to George, Ben, and Christopher for not being there, and Jonny Davies for circumventing BA security measures to save this article.

## *References*


Almeida, R.A., Matthews, K.R., Cifrian, E., et al. 1996. *Staphylococcus aureus* invasion of bovine mammary epithelial cells. J Dairy Sci 79:1021–6.

Altemeier, W.A., Hummel, R.P., and Hill, E.O. 1963. Staphylococcal enteritis following therapy. Ann Surg 157:847–58.

Andrews, M.-M., Parent, E.M., Barry, M., and Parsonnet, J. 2001. Recurrent non-menstrual toxic shock syndrome: Clinical manifestations, diagnosis, and treatment. Clin Infect Dis 32:1471–9.

Anonymous. 1999. Four paediatric deaths from community-acquired MRSA—Minnesota and North Dakota, 1997–1999. MMWR 48:707–10.

Beaber, J.W., Hochhut, B., and Waldor, M.K. 2004. SOS response promotes horizontal dissemination of antibiotic resistance genes. Nature 427:72–4.

Bernardo, K., Pakulat, N., Fleer, S., et al. 2004. Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. Antimicrob Agents Chemother 48:546–55.

Bhakdi, S., and Tranum-Jensen J. 1991. Alpha-toxin of *Staphylococcus aureus*. Microbiol Rev 55:733–51.

Bisognano, C., Vaudaux, P.E., Lew, D.P., Ng, E.Y.W., and Hooper, D.C. 1997. Increased expression of fibronectin-binding proteins by fluoroquinolone-resistant *Staphylococcus aureus* exposed to subinhibitory levels of ciprofloxacin. Antimicrob Agents Chemother 41:906–13.

Brouillette, E., Martinez, A., Boyll, B.J., Allen, N.E., and Malouin, F. 2004. Persistence of a *Staphylococcus aureus* small-colony variant under antibiotic pressure. FEMS Immunol Med Microbiol 41: 35–41.

Butcher, W.G., Close, J., Krajewska-Pietrasik, D., and Switalski, L.M. 1994. Antibiotics alter interactions of *Staphylococcus aureus* with collagenous substrata. Chemotherapy 40:114–23.

Chuard, C., Vaudaux, P.E., Proctor, R.A., and Lew, D.P. 1997. Decreased susceptibility to antibiotic killing of a stable small colony variant of *Staphylococcus aureus* in fluid phase and on fibronectin-coated surfaces. J Antimicrob Chemother 39:603–8.

Dancer, S.J. 2001. The problem with cephalosporins. J Antimicrob Chemother 48:463–78.

Dancer, S.J. 2004. How antibiotics can make us sick: The less obvious effects of antimicrobial chemotherapy. Lancet Infect Dis 4: 611–9.

Donabedian, H. 2003. Quorum sensing and its relevance to infectious diseases. J Infect 46: 207–14.

Donlan, R.M. 2002. Biofilms: Microbial life on surfaces. Emerg Infect Dis 8: 881–90.

Dostal, R.E., Seale, J.P., and Yan, B.J. 1992. Resistance to ciprofloxacin of respiratory pathogens in patients with cystic fibrosis. Med J Aust 156: 20–4.

Drummond, L.J., Smith, D.G.E., and Poxton, I.R. 2003. Effects of sub-MIC concentrations of antibiotics on growth of and toxin production by *Clostridium difficile*. J Med Microbiol 52: 1033–8.

Farrell, R.J., and LaMont, J.T. 2000. Pathogenesis and clinical manifestations of *Clostridium difficile* diarrhea and colitis. Curr Top Microbiol Immunol 250: 109–25.

Feder, H.M. 2000. Methicillin-resistant *Staphylococcus aureus* infections in 2 pediatric patients. Arch Fam Med 9: 560–2.

Finch, R.G., Pritchard, D.I., Bycroft, B.W., Williams, P., and Stewart, G.S.A.B. 1998. Quorum sensing: A novel target for anti-infective therapy. J Antimicrob Chemother 42: 569–71.

Gabello, M., and Iglewski, B.H. 1991. Cloning and characterization of the *Pseudomonas aeruginosa lasR* gene, a transcriptional activator of elastase production. J Bacteriol 173: 3000–9.

Goerke, C., Koller, J., and Wolz, C. 2006. Ciprofloxacin and trimethoprim cause phage induction and virulence modulation in *Staphylococcus aureus*. Antimicrob Agents Chemother 50: 171–7.

Gorske, B.C., and Blackwell, H.E. 2006. Interception of quorum sensing in *Staphylococcus aureus*: A new niche for peptidomimetics. Org Biomol Chem 4: 1441–5.

Harbarth, S., Garbino, J., Pugin, J., Romand, J.A., Lew, D., and Pittet, D. 2003. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 115: 529–35.

Hastings, P.J., Rosenberg, S.M., and Slack, A. 2004. Antibiotic-induced lateral transfer of antibiotic resistance. Trends Microbiol 12: 401–4.

He, P., Li, N., and Li, S. 2001. A study on beta-lactamase activity of biofilm *Escherichia coli*. Zhonghua Jie He He Hu Xi Za Zhi 24: 537–8.

Herbert, S., Barry, P., and Novick, R.P. 2001. Subinhibitory clindamycin differentially inhibits transcription of exoprotein genes in *Staphylococcus aureus*. Infect Immun 69: 2996–3003.

Hingley, S.T., Hastie, A.T., Kueppers, F., et al. 1986. Effect of ciliostatic factors from *Pseudomonas aeruginosa* on rabbit respiratory cilia. Infect Immun 51: 254–62.

Horii, T., Muramatsu, H., Monji, A., and Miyagishima, D. 2005. Release of exotoxin A, peptidoglycan and endotoxin after exposure of clinical *Pseudomonas aeruginosa* isolates to carbapenems in vitro. Chemotherapy 51: 324–31.

Hurley, J.C. 1992. Antibiotic induced release of endotoxin: A reappraisal. Clin Infect Dis 15: 840–54.

Ismaeel, A., Senok, A.C., Bindayna, K.M., et al. 2005. Effect of antibiotic subinhibitory concentration on cytolethal distending toxin production by *Campylobacter jejuni*. J Infect 51: 144–9.

Ji, G., Beavis, R.C., and Novick, R.P. 1995. Cell density control of staphylococcal virulence mediated by an octapeptide pheromone. Proc Natl Acad Sci USA 92: 12055–9.

Kain, K.C., Schulzer, M., and Chow, A.W. 1993. Clinical spectrum of non-menstrual toxic shock syndrome (TSS) comparison with menstrual TSS by multivariate discriminant analyses. Clin Infect Dis 16:100–6.

Keren, I., Kaldalu, N., Spoering, A., Wang, Y., and Lewis, K. 2004. Persister cells and tolerance to antimicrobials. FEMS Microbiol Lett 230: 3–18.

Kernodle, D.S., McGraw, P.A., Barg, N.L., et al. 1995. Growth of *Staphylococcus aureus* with nafcillin in vitro induces alpha-toxin production and increases the lethal activity of sterile broth filtrates in a murine model. J Infect Dis 172: 410–19.

Kernodle, D.S., Classen, D.C., Stratton, C.W., and Kaiser, A.B. 1998. Association of borderline oxacillin-susceptible strains of *Staphylococcus aureus* with surgical wound infections. J Clin Microbiol 36: 219–22.

Klugman, K.P. 2003. Implications for antimicrobial prescribing of strategies based on bacterial eradication. Int J Infect Dis 7 (Suppl 1): S27–31.

Kodama, T., Santo, T., Yokoyama, T., et al. 1997. Postoperative enteritis caused by methicillin-resistant *Staphylococcus aureus*. Surg Today 27: 816–25.

Kollef, M.H. 2003. Appropriate empirical antibacterial therapy for nosocomial infections. Drugs 63: 2157–68.

Koszczol, C., Bernardo, K., Kronke, M., and Krut, O. 2006. Subinhibitory quinupristin/dalfopristin attenuates virulence of *Staphylococcus aureus*. J Antimicrob Chemother 58: 564–74.

Krut, O., Sommer, H., and Kronke, M. 2004. Antibiotic-induced persistence of cytotoxic *Staphylococcus aureus* in non-phagocytic cells. J Antimicrob Chemother 52: 167–73.

Langsrud, S., Sidhu, M.S., Heir, E., and Holck, A.L. 2003. Bacterial disinfectant resistance—A challenge for the food industry. Int Biodeterioration Biodegrad 51: 283–90.

LeBlanc, L., Pepin, J., Toulouse, K., Ouellette, M.-F., Coulombe, M.-A., Corriveau, M.-P., and Alary, M.-E. 2006. Fluoroquinolones and risk for methicillin-resistant *Staphylococcus aureus*, Canada. Emerg Infect Dis 12. Available from http://www.cdc.gov/ncidod/EID/vol12no09/06-0397.htm (last accessed 14 September 2006).

Lindsay, D., and von Holy, A. 2006. Bacterial biofilms within the clinical setting: What healthcare professionals should know. J Hosp Infect 64:313–25.

Lorian, V., and Gemmell, G.C. 1991. Effect of low antibiotic concentrations on bacteria: Effects on ultrastructure, virulence, and susceptibility to immunodefenses, in Lorian, V. (ed). Antibiotics in Laboratory Medicine. Baltimore, Williams & Wilkins, pp. 493–555.

Lundén, J., Autio, T., Markkula, A., Hellström, S., and Korkeala, H. 2003. Adaptive and cross-adaptive responses of persistent and non-persistent *Listeria monocytogenes* strains to disinfectants. Int J Food Microbiol 82: 265–72.

Maiques, E., Ubeda, C., Campoy, S., et al. 2006. β-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*. J Bacteriol 188: 2726–9.

Mason, B.W., Howard, A.J., and Magee, J.T. 2003. Fusidic acid resistance in community isolates of methicillin-susceptible *Staphylococcus aureus* and fusidic acid prescribing. J Antimicrob Chemother 51: 1033–6.

Meyer, B. 2003. Approaches to prevention, removal and killing of biofilms. Int Biodeterioration Biodegrad 51: 249–53.

Morrison, D.A. 1997. Streptococcal competence for genetic transformation: Regulation by peptide pheromones. Microb Drug Resist 3: 27–37.

Muller, A., Thouverez, M., Talon, D., and Bertrand, X. 2003. Contribution of antibiotic pressure in the acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA) in a university hospital. Pathol Biol 51: 454–9.

Nelson, J.M., Smith, K.E., Vugia, D.J., et al. 2004. Prolonged diarrhea due to ciprofloxacin-resistant campylobacter infection. J Infect Dis 190: 1150–7.

Ohlsen, K., Ziebuhr, W., Koller, K.-P., Hell, W., Wichelhaus, T.A., and Hacker, J. 1998. Effects of subinhibitory concentrations of antibiotics on alpha-toxin (hla) gene expression of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* isolates. Antimicrob Agents Chemother 42: 2817–23.

Pechere, J.C. 1989. Resistance to third generation cephalosporins: The current situation. Infection 17: 333–7.

Pepin, J., Valiquette, L., Alary, M.-E., et al. 2004. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: A changing pattern of disease severity. Can Med Assoc J 171: 466–72.

Proctor, R.A., Olbrantz, P.J., and Mosher, D.F. 1983. Subinhibitory concentrations of antibiotics alter fibronectin binding to *Staphylococcus aureus*. Antimicrob Agents Chemother 24: 823–6.

Recse, P., Kreiswirth, B., O'Reilly, M., Schlievert, P., Gruss, A., and Novick, R.P. 1986. Regulation of exoprotein expression in *Staphylococcus aureus* by agar. Mol Gen Genet 202: 58–61.

Renzoni, A., Francois, P., Li, D., et al. 2004. Modulation of fibronectin adhesins and other virulence factors in a teicoplanin-resistant derivative of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 48: 2958–65.

Sakoulas, G., Gold, H.S., Cohen, R.A., Venkataraman, L., Moellering, R.C., and Eliopoulos, G.M. 2006. Effects of prolonged vancomycin administration on methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with recurrent bacteraemia. J Antimicrob Chemother 57: 699–704.

Sanyal, S.C., and Mokaddas, E.M. 1999. The increase in carbapenem use and emergence of *Stenotrophomonas maltophilia* as an important nosocomial pathogen. J Chemother 11: 28–33.

Schrader-Fischer, G., and Berger-Bachi, B. 2001. The AbcA transporter of *Staphylococcus aureus* affects autolysis. Antimicrob Agents Chemother 45: 407–12.

Sendi, P., Rohrbach, M., Graber, P., Frei, R., Ochsner, P.E., and Zimmerli, W. 2006. *Staphylococcus aureus* small colony variants in prosthetic joint infection. Clin Infect Dis 43: 961–7.

Seral, C., Barcia-Macay, M., Migeot-Leclercq, M.P., Tulkens, P.M., and Van Bambeke, F. 2005. Comparative activity of quinolones (ciprofloxacin, levofloxacin, moxifloxacin and garenoxacin) against extracellular and intracellular infection by *Listeria monocytogenes* and *Staphylococcus aureus* in J774 macrophages. J Antimicrob Chemother 55: 511–7.

Shramm, G.E., Johnson, J.A., Doherty, J.A., Micek, S.T., and Kollef, M.H. 2006. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: The importance of appropriate initial antimicrobial treatment. Crit Care Med 34: 2069–74.

Taylor, C.M., Riordan, F.A.I., and Graham, C. 2006. New football boots and toxic shock syndrome. BMJ 332: 1376–8.

Tenke, P., Kovacs, B., Jäckel, M., and Nagy, E. 2006. The role of biofilm infection in urology. World J Urol 24: 13–20.

Van der Waaij, D. 1987. Colonisation resistance of the digestive tract—Mechanism and clinical consequences. Nahrung 31: 507–17.

Varma, J.K., Molbak, K., Barrett, T.J., et al. 2005. Antimicrobial-resistant nontyphoidal Salmonella is associated with excess bloodstream infections and hospitalisations. J Infect Dis 191: 554–61.

Vaudaux, P.E., Monzillo, V., Francois, P., Lew, D.P., Foster, T.J., and Berger-Bachi, B. 1998. Introduction of the mec element (methicillin resistance) into *Staphylococcus aureus* alters in vitro functional activities of fibrinogen and fibronectin adhesins. Antimicrob Agents Chemother 42: 564–70.

Vaudaux, P., Kelley, W.L., and Lew, D.P. 2006. *Staphylococcus aureus* small colony variants: Difficult to diagnose and difficult to treat. Clin Infect Dis 43: 968–70.

Venezia, R.A., Domaracki, B.E., Evans, A.M., Preston, K.E., and Graffunder, E.M. 2001. Selection of high-level oxacillin resistance in heteroresistant *Staphylococcus aureus* by fluoroquinolone exposure. J Antimicrob Chemother 48: 375–81.

Weber, S.G., Gold, H.S., Hooper, D.C., Karchmer, A.W., and Carmeli, Y. 2003. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalised patients. Emerg Infect Dis 9: 1415–22.

Wey, S.B., Mori, M., Pfaller, M.A., Woolson, R.F., and Wenzel, R.P. 1989. Risk factors for hospital-acquired candidemia. A matched case control study. Arch Intern Med 149: 2349–53.

Williams, I., Venables, W.A., Lloyd, D., Paul, F., and Critchley, I. 1997. The effects of adherence to silicone surfaces on antibiotic susceptibility in *Staphylococcus aureus*. Microbiol 143: 2407–13.

Worlitzsch, D., Kaygin, H., Steinhuber, A., Dalhoff, A., Botzenhart, K., and Doring, G. 2001. Effects of amoxicillin, gentamicin, and moxifloxacin on the haemolytic activity of *Staphylococcus aureus* in vitro and in vivo. Antimicrob Agents Chemother 45: 196–202.

Zhang, X., McDaniel, A.D., Wolf, L.E., Keusch, G.T., Waldor, M.K., and Acheson, D.W. 2000. Quinolone antibiotics induce Shiga toxin-encoding bacteriophages, toxin production, and death in mice. J Infect Dis 181: 664–70.

*This page intentionally blank*

# Chapter 2
# The Process of Antibiotic Prescribing: Can It Be Changed?

Jos W.M. van der Meer and Richard P. T. M. Grol

The desire to digest medicines is one of the principal features which distinguish men from animals.

—Sir William Osler

## Introduction

Antibiotics are among the most successful drugs in medicine. Their power in therapy as well as in prophylaxis was so convincing that for most of the older antibiotics, controlled clinical trials were never performed. The advent of antibiotics dramatically altered the prognosis of bacterial infections, such as streptococcal endocarditis, purulent meningitis, and sepsis caused by staphylococci and Gram-negative bacteria. From a historical point of view the ability to prescribe antibiotics changed the therapeutic power of physicians in an unprecedented fashion. Although antibiotics have lost quite a bit of their glamour due to increasing antimicrobial resistance of microorganisms, this sense of power probably still underlies antibiotic prescribing. This may be one of the reasons why inappropriate antibiotic prescribing behavior of physicians is common and hard to change. Changing these prescribing habits is necessary, since worldwide inappropriate, excessive use of antibiotics has led to the growing problem of resistance.

In this chapter, we will explore prescribing habits and obstacles and the ways to change these.

## Use of Antibiotics

Antibiotics for human use are prescribed in general practice and in hospitals. In the Netherlands (a country of nearly 16.5 million inhabitants) in the year 2000, 86% of the 5.7 million antibiotic prescriptions were issued by general practitioners. It is of interest that there are some regional differences in the number of prescriptions per patient per year (ranging from 0.36 to 0.45). Such differences are not well explained.[1] Antibiotic use in the Netherlands is the lowest in Europe[2,3]; usage is 4 times higher in

France, 3 times higher in Belgium and Italy, and 1.5 times higher in Germany.[2,3] Not only the relative numbers of prescription vary, but also the extent to which broad spectrum and newer antibiotics are being prescribed.

The rates of antimicrobial resistance in Europe parallel the numbers of prescriptions. The reasons for differences in prescribing habits between countries are not simple. Not only does the way medical professionals think and act play a role, also patient knowledge and behavior, organization of patient care, health insurance, and, last but probably not least, sociocultural environment of both physicians and patients are important determinants.[4] These determinants will be discussed in more detail.

## Medical Professionals

Some of the factors that may lead to suboptimal prescribing of antibiotics are listed in Table 2.1.

A major factor is imperfect knowledge of the prescriber. This lack of knowledge has to do with insufficient knowledge of infectious diseases, the potential causative microorganisms and their susceptibility to antimicrobials, and expertise on antimicrobial drugs. With regard to the latter, there is probably too little emphasis in most medical curricula on the relevance of prudent antibiotic prescribing. Imperfect knowledge of infectious diseases leads to insecurity about the diagnosis and difficulties of distinguishing in the clinic between bacterial and viral infections. Apparently, many physicians do not know (or ignore) that antibiotics do not influence the outcome in most cases of common infections such as otitis media, sinusitis, acute bronchitis, and chronic obstructive pulmonary disease.[5–9] In a series of elegant studies Holmes et al. showed that antibiotics do not alter the natural course of "cough."[10] Poor case definition also in the hospital setting will lead to indiscriminate use of antibiotics.[11,12]

Many doctors tend to take the route of certainty rather than the uncertain one. Many years ago, Dr. Calvin Kunin called antibiotics "drugs of fear."[13]

In discussions on whether antibiotics are indicated or not, the fear of complications if one refrains from prescribing an antibiotic is often put forward.[14,15] Examples are the fear of development of mastoiditis if otitis media is not treated, of pneumonia if acute bronchitis is not treated. Fear of being sued for not prescribing an antibiotic is more common in the United States than in Europe.

TABLE 2.1. Professional factors that may lead to suboptimal prescribing

| |
|---|
| Imperfect knowledge |
| Diagnostic uncertainty |
| Fear of complications |
| Fear of disciplinary cases |
| Communicative aspects |
| Perceived patient expectations |
| Financial interests |

In an interview study by MacFarlane et al.,[16] it was found that doctors felt that probably some 20% of patients with bronchial infections needed antibiotics, but that nonclinical factors determined whether antibiotics were given. Antibiotics were prescribed more commonly to patients from deprived areas and female patients. Pressure exerted on doctors by patients or perceived expectations of patients are major factors that determine prescription. This is probably a global problem.[15] Doctors who think that a patient expects an antibiotic will diagnose a bacterial infection more often and more frequently prescribe an antibiotic.[17]

Patients who expect an antibiotic are 3 times more likely to be prescribed an antibiotic than patients who do not[18,19]; if the doctor thinks that the patient wants an antibiotic, a prescription is given 7 to 10 times more often.

An interesting study by Mangione-Smith et al. demonstrates that physicians' perceptions of parental expectations for antibiotics increased when parents questioned the doctor's treatment plan.[17] Grob has pointed out that a series of contextual factors may play a role in the process of prescribing.[20]

We should not forget that providing a prescription may also have a symbolic meaning: by marking the end of the consultation.

It is an important question whether we can change prescribing habits. It is generally perceived that clinical behavior is notoriously difficult to change and as noted in the introduction to this chapter, it may be even more difficult for antibiotics. Programs aiming at altering physicians' behavior have reached improvements in a very modest range (5–10%).[21] Sbarbaro[22] describes that changing physician behavior is viewed by many as "an exercise in futility—an unattainable goal intended only to produce premature aging in those seeking the change." He adds that the more optimistic view might describe the process as uniquely challenging.

From the literature it is clear that a multifaceted approach is needed to influence prescribing of doctors.[21,23,24] Education of doctors, feedback about prescribing (with or without comparison to colleagues), financial incentives or sanctions, organizational and logistic measures, regulations, and other measures may have some effect if attuned to the problem.[23] Welschen[24] performed a systematic review of measures attempting to change antibiotic prescribing for bronchial infections in general practice. Eight studies qualified for that review because these evaluated all kinds of measures (group education, feedback, information for patients, and individual education for the practitioner). Most measures had a small effect (average 6%).

It is clear that traditional education has little if any effect. Greater effects are seen from computerized decision support, in which the computer feeds back messages about proper or improper antibiotic use.[25] Another approach is that using outreach visitors, specially trained persons who support and inform practitioners on a one-to-one basis.[26,27] Significant reductions in prescribing have been reported using this method. In a combined approach (patient education, feedback to doctors, and outreach visitors), a 35% reduction in prescription was detected.[28]

An interesting intervention is that in which patients receive a prescription with the explicit instruction only to collect and swallow the drug if they are convinced that they need it. Reductions of 25–54% have been found with these "delayed" prescriptions.[29,30]

## Patient Knowledge and Behavior

The final paragraphs of the preceding section already alluded to the important role patients play in the prescribing process. A series of patient-related factors are implicated in determining the quality of antimicrobial prescribing (Table 2.2), First, the level of knowledge regarding the difference between viral and bacterial infections, regarding the antimicrobial resistance problem and the effectiveness of antibiotics is important.[31,32] It has been found that 83% of Canadians were unfamiliar with the concept of antimicrobial resistance, and this was especially the case for poorly educated young people.[22] An investigation carried out in the United States showed that 27% of patients with a cold thought that an antibiotic would help, 58% were unaware of the risks of antibiotic treatment, and 48% expected an antibiotic prescription.[33] MacFarlane et al.[16] in the United Kingdom showed that 87% of patients with bronchitis thought they had an infection, 72% wanted an antibiotic and expected a prescription; only 19% explicitly asked for a prescription.

In a study among patients in the Netherlands, it was found that patients with bronchial infections who expected an antibiotic had a 66% probability of receiving an antibiotic, whereas patients without such expectation had only a 34% probability.[24]

It is clear from these data that addressing patients, future patients, parents and carers of children, teachers, and staff of day-care centers about antibiotic use is a logical step. Nowadays, there are large scale programs, using the mass media, in which consistent messages are brought forward. These messages are:

- antibiotics do not work against viruses;
- resistance against antibiotics is a growing problem with serious risks;
- hygienic measures, like handwashing, help to prevent infections.

Such programs have been launched in Canada, Belgium, the United Kingdom, Australia, and the United States.[22] That such programs may be successful may be derived from the following examples. The Canadian program "Do bugs need drugs?" showed a reduction in the use of antibiotics and increased the use of first-line drugs. The American program aiming at doctors and parents of young children led to an 11% decrease in antibiotic use.[33] The Belgian national program was followed by a 26% drop in use of antibiotics.

TABLE 2.2. Patient factors that may lead to suboptimal prescribing

| |
|---|
| Lack of knowledge regarding bacterial and viral infections |
| Notions of the effectiveness of antibiotics |
| Expectation of being given a prescription |
| Satisfaction when given a prescription |
| Compliance with the prescription |

## Organization of Patient Care

The way patient care is organised also has an influence on antibiotic prescribing. Although research in this area is scarce, it is conceivable that factors like coordination of care, collaboration and communication between professionals, teamwork, the logistics of care, control and review systems may play a role.[32] These aspects are of importance in general practice as well as in the hospital setting. In hospitals, different disciplines are usually involved in antibiotic prescribing (clinicians, nurses, pharmacists, microbiologists), but the degree to which protocols and control systems (such as antibiotic formulary, limited permission to prescribe certain antibiotics, antibiotic order forms, automatic stop orders, antibiotic consultation) are in place greatly differs between hospitals. Although the effectiveness of formularies and control measures has been the subject of many studies, the methodological robustness of many of these studies is limited, according to a Cochrane review.[34,35] Nevertheless there is a worldwide tendency to standardize treatment in protocols. This also holds for antibiotic treatment and nowadays more and more protocols are evidence based and for instance evaluated using the AGREE instrument.[36]

An important issue is the compliance of doctors with such protocols. Research in this area shows a gloomy picture: protocols are usually not closely followed for a variety of reasons that will be detailed below.[37–39]

Guidelines and protocols to improve antibiotic prescribing, mostly limited to a group of conditions (e.g., community-acquired pneumonia, sexually transmitted diseases), have been issued by professional societies, by governmental bodies in many countries, and by hospital committees. Until recently, the authorities issuing such guidelines addressed doctors, but did not seem to worry about implementation. It has become increasingly clear that implementation needs efforts and even then it will meet with a large number of barriers. In their seminal paper, Cabana et al. describe the major barriers in the implementation of guidelines.[39] These barriers, which can or cannot be changed, are located within the system, the physician, and the patient. Within the system there are lack of resources, lack of time, organizational constraints, and other persons in the system. With respect to the barriers in doctors, these authors distinguish between knowledge, attitude, and behavior, and for each of these areas special measures are needed. It is laborious to identify these barriers in practice, and even harder to overcome them. Despite great efforts the effects are limited as we experienced in a multihospital intervention in respiratory tract infections.[38,40,41]

## Sociocultural Environment

There is growing awareness that the sociocultural and socioeconomic context plays a role in the prescribing pattern of drugs such as antibiotics. Cultural factors seem to play a major role in this area. In this context, the ideas that

patients and also healthy people within a society have about the health, causes of disease, labeling of illness, attributions, coping strategies, and treatment modalities may well be decisive. As an interesting example, differences observed between the Netherlands and Belgium may serve. Deschepper and Van der Stickele[42] found that in the Netherlands, people label a bronchial infection as a cold for which they usually take an aspirin or just wait. In Belgium, people label this ailment as bronchitis, they do not decide how to deal with it themselves, but tend to consult a doctor. In the Netherlands, people do not look up to their general practitioner, whereas in Belgium they do: they expect the doctor to make a decision. In Germany the situation is somewhat different: patients tend to have a wait-and see attitude to bronchial infections, they will avoid antibiotics and prefer homeopathic medication.[43] In France, patients commonly visit their doctor to receive an antibiotic prescription; to that end they put their doctor under great pressure.

According to Deschepper and Van der Stickele,[42] use of antibiotics in a country relates to a number of local cultural characteristics. Such characteristics have been described in an anthropological study by Hofstede, carried out in 50 countries among employees of IBM.[44] Hofstede describes major differences between countries with regard to concepts such as “power distance” (the extent to which those with less power in a society expect and accept that power is unevenly distributed). In a hierarchical society there is a high power distance, whereas in an egalitarian society power distance is low. Another characteristic is “uncertainty avoidance” (the extent to which members of a culture feel threatened by uncertain or unknown situations; willingness to accept uncertainty and risks, tendency to avoid any lack of clarity).

Interestingly, Deschepper and Van der Stickele[42] found a correlation of 0.83 between power distance and antibiotic use: more power distance is associated with more antibiotic use. The correlation between uncertainty avoidance and antibiotic use showed a correlation of 0.70, more antibiotic use associated with more uncertainty avoidance. As stated at the beginning of this chapter, antibiotics are drugs of fear and have a defensive function: the prescriber and the patient go for certainty, the prescriber wants to control everything and wants to avoid complications, the patient adapts to this approach by leaving decisions to the physician.

In a study by one of us,[45] it was found that Belgian and Dutch general practitioners greatly differ in dealing with uncertainties and risks. Another Dutch study of therapeutic drug use in Europe confirms that countries with an egalitarian society (the Netherlands, United Kingdom, Scandinavia) have lower usage levels than countries with a hierarchical society (France, Italy Spain, Portugal, Greece).[46] It is remarkable that the differences in use coincide with differences in religion: countries with traditionally a predominantly Protestant population tend to have lower usage than those with a predominantly Catholic population.[46] This is perhaps not surprising as attitude to disease and treatment are closely linked to religious background.

## Socioeconomic Environment: The Role of Industry

The way health care is funded also clearly has an impact on antibiotic prescribing. A good example can be found in the study of Harbarth et al.,[43] in which the French situation at that time was compared to that in Germany. In France the prices of drugs were low and by means of extremely aggressive marketing, the pharmaceutical industry tried to compensate for this. Pharmacies, however, received more reimbursement for expensive drugs such as broad-spectrum antibiotics. There is a trend to avoid generic drugs and to use new drugs rather than older ones.

In Belgium, a change in the reimbursement profoundly affected the antibiotic use pattern especially for prophylactic antibiotics in surgery. Whereas originally Belgian doctors often prescribed prolonged courses of sophisticated antibiotics for surgical prophylaxis, the change in reimbursement in 1997 has led to a rapid implementaton of optimized antibiotic prophylaxis.[47]

Another element here is the role of the pharmaceutical industry. We already alluded to the marketing strategies in France. Pharmaceutical industry promotes its products in a variety of ways. One way is to try to influence the prescribing habits of doctors. The policies used for this range from very direct "aggressive" pressure, with rewards or even "bribes," to more subtle and indirect techniques. Although many doctors claim that they do not feel influenced in their prescribing habits, research in this area has reached other conclusions.[48]

A recent example of aggressive marketing was seen in Belgium. Following a broadcasting about the danger of emergence of resistance with indiscriminate use of antibiotics, a pharmaceutical industry marketing a new fluoroquinolone instantaneously responded with a campaign pointing out that their new quinolone was the drug of choice to combat resistant organisms (W. Peetermans personal communication).

Of great concern in this respect is the situation in Eastern Europe. The countries in Eastern Europe have been deprived of modern antibiotics for decades, and thus selection pressure on microorganisms was limited compared to more privileged parts of the world. However, there is now a rapid increase in antimicrobial resistance in these countries, most probably due to large scale and indiscriminate use of newer antibiotics. Although exact data on antibiotic usage and drug promotion by the pharmaceutical industry are lacking, it is likely that there is intensive marketing going on in this part of the world, and that this significantly contributes to the problem.

With the increasing importance of guidelines for clinical practice, it is evident that from a point of view of marketing, it is important for industry to influence the development of guidelines. This does not occur only for antibiotic therapy, but also for other guidelines. It turns out that 87% of authors of guidelines have ties with industry and these are often not revealed.[49]

At another level, industry funds clinical trials on drugs, and there is no doubt that this has influenced at least the published results. Again, this does not

pertain only to antimicrobial drugs. As Kjaergard and Als-Nielsen have pointed out, authors of trials with competing interests, i.e., those funded by for-profit organizations, are significantly more positive toward the results of the intervention that was investigated than those without.[50] Recently there have been a couple of initiatives to regulate the interaction between the pharmaceutical industry and prescribers. One example are the stringent Yale guidelines which ban faculty from receiving any form of gift, meal, or free drug sample from industry, and set more stringent standards for the disclosure and resolution of financial conflict of interest in Yale's educational programs.[51] To limit unwanted influences in drug trials, an international initiative of a clinical trial register and full disclosure of the role of industry therein has been taken (www.controlled-trials.com/isrctn)

The Royal Netherlands Academy of Arts and Sciences (KNAW) recently voiced its concern about the independence of the investigator and has proposed a code of conduct to be signed by the body that commissioned the investigation and the researcher.[52]

A final point of concern is the availability of antibiotics as over-the-counter drugs (OTC); this is common practice in many countries, either legal or illegal. Especially for antibiotics, availability as OTC violates all aspects of careful prescribing (diagnosis of infection, selection of drug, correct dose, and duration of therapy) and has a sizable impact on development of resistance. A relatively new threat is the availability of antimicrobial drugs via the Internet.

So far, little has been done at a global scale to limit the over the counter availability of antimicrobial drugs. Here lies a great challenge, which is hard to tackle since the economic interests are immense. The same holds for the sales through the Internet.

## Conclusions

There is an urgent need to try to improve antibiotic prescribing worldwide. Changing prescribing and antibiotic use is a challenge of formidable complexity, in which—as pointed out in this chapter—many factors play a role: those related to professionals, patients, organisation of patient care and those within the social cultural and economic context. Our current knowledge of the relative weight of each of these factors is still too limited and there is a need to obtain more insight into what would be optimal strategies to tackle these problems. The current wisdom is that a multifaceted program with activities at different levels is most successful, but also here the success of such strategies is strongly dependent on the setting (primary care or hospital setting), country, and culture.

*Acknowledgment*. We wish to thank Professor P De Smet for his help.

## *References*


1. Baart F, de Neeling A. Antibioticagebruik buiten het ziekenhuis. Pharm Weekbl 2001;136(22):786–90.
2. Cars O, Mokstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851–3.
3. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. Lancet 2005;365:579–87
4. Grol R, Wensing M, Eccles M. Improving Patient Care. Implementation of Change in Clinical Practice. Oxford; Elsevier, 2005.
5. van Buchem FL, Dunk JH, van't Hof MA. Therapy of acute otitis media: Myringotomy, antibiotics, or neither? A double-blind study in children. Lancet 1981;2:883–7.
6. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet 1997;349:683–7.
7. Stalman W, van Essen GA, van der Graaf Y, de Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial. Br J Gen Pract 1997;47:794–9.
8. Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis? Lancet 1995;345:665–6.
9. Nicotra MB, Kronenberg RS. Con: Antibiotic use in exacerbations of chronic bronchitis. Semin Respir Infect 1993;8:254–8.
10. Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. Br J Gen Pract 2001;51:177–81.
11. Moss FM, McNicol MW, McSwiggan DA, Miller DL.Survey of antibiotic prescribing in a district general hospital. II. Lower respiratory tract infection. Lancet 1981;2:407-
12. Moss FM, McNicol MW, McSwiggan DA, Miller DL. Survey of antibiotic prescribing in a district general hospital. III. Urinary tract infection. Lancet 1981;2:461–2.
13. Kunin CM, Tupasi T, Craig WA. Use of antibiotics. A brief exposition of the problem and some tentative solutions. Ann Intern Med 1973;79:555–60.
14. Cho H, Hong S, Park S. Knowledge and beliefs of primary care physicians, pharmacists, and parents on antibiotic use for the pediatric common cold. Soc Sci Med 2004;58:623–9.
15. Kunmar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ 2003;326:138–43.
16. MacFarlane J, Holmes W, MacFarlane R, Britten N. Influence of patients expectations on antibiotic management of acute lower respiratory tract illness in general practice: Questionnaire study. BMJ 1997;315:1211–4.
17. Mangione-Smith R, McGlynn EA, Elliott MN, Krogstad P, Brook RH. The relationship between perceived parental expectations and pediatrician antimicrobial prescribing behavior. Pediatrics 1999;103:711–8.
18. Britten N, Ukoumunne OC. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: A questionnaire survey. BMJ 1997;315:1506–10.
19. Cockburn J, Pitt S. Prescribing patterns in clinical practice: Patients' expectations and doctors'perception of patient expectations: A questionnaire study. BMJ 1997;315:520–3.

20. Grob PR. Antibiotic prescribing practices and patient compliance in the community. Scand J Infect Dis Suppl 1992;83:7–14.
21. Grol R, Grimshaw J. From best evidence to best practice: Effective implementation of change in patients'care. Lancet 2003;362:1225–30.
22. Sbarbaro JA. Can we influence prescribing patterns? Clin Infect Dis 2001;33:S240–4.
23. Finch R, Metlay J, Davey P, Baker L on behalf of the International Forum on Antibiotic Resistance. Educational interventions to improve antibiotic use in the community: Report from the International Forum on Antibiotic Resistance (IFAR) colloquium 2002. Lancet Infect Dis 2004;4:44–53.
24. Welschen I. Prescribing antibiotics for acute respiratory tract infections in primary care. Utrecht University, PhD thesis, 2004.
25. Pestotnik SL, Classen DC, Evens RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: Clinical and financial outcomes. Ann Intern Med 1996;124:884–90.
26. Soumerai SB, McLaughlin TJ, Avorn J. Improving drug prescribing in primary care: A critical analysis of the experimental literature. Milbank Q 1989;67(2):268–317.
27. Thomson M, Oxman A, Davis D, et al. Outreach visits to improve health professional practice and health care outcomes. The Cochrane Library. Issue 3, Oxford, Update Software, 1998.
28. Gonzales R, Steiner JF, Lum A, Barrett PH Jr.Decreasing antibiotic use in ambulatory practice: Impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. JAMA 1999;281:1512–9
29. Edwards M, Dennison J, Sedgwick P. Patients' responses to delayed antibiotic prescription for acute upper respiratory tract infections. Br J Gen Pract 2003;53:845–50.
30. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. Br J Gen Pract 2003;53:871–7.
31. Belongia E, Naimi T, Gale C, Besser R. Antibiotic use and upper respiratory infection: A survey of knowledge, attitudes, and experiences in Wisconsin and Minnesota. Prevent Med 2002;34(3):346–52.
32. Fine JM, Fine MJ, Galusha D, Petrillo M, Meehan TP. Patient and hospital characteristics associated with recommended processes of care for elderly patients hospitalized with pneumonia: Results from the medicare quality indicator system pneumonia module. Arch Intern Med 2002;162:827–33.
33. Perz J, Craij A, Coffey C, Jorgensen D, Mitchel E, Hall S, Schaffner W, Griffin M. Changes in antibiotic prescribing for children after a community-wide campaign. JAMA 2002;287:3103–9.
34. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement:A systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. J Antimicrob Chemother 2003;52:764–71.
35. Davey P, Brown E, Hartman G. Systematic review of interventions to change antibiotic prescribing to hospital inpatients. Protocol Cochrane Review EPOC 2004.
36. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: The AGREE project. Qual Saf Health Care 2003;12:18–23.
37. van Kasteren ME, Mannien J, Kullberg BJ, de Boer AS, Nagelkerke NJ, Ridderhof M, Wille JC, Gyssens IC. Quality improvement of surgical prophylaxis in Dutch hospitals: Evaluation of a multi-site intervention by time series analysis. J Antimicrob Chemother 2005;56:1094–102

38. Schouten JA. Improving the quality of antibiotic use for respiratory tract infections at hospitals. PhD thesis, Radboud University, Nijmegen, the Netherlands, 2006.
39. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458–65.
40. Schouten JA, Hulscher ME, Kullberg BJ, Cox A, Gyssens IC, van der Meer JW, Grol RP. Understanding variation in quality of antibiotic use for community-acquired pneumonia: Effect of patient, professional and hospital factors. J Antimicrob Chemother 2005;56:575–82.
41. Schouten JA, Hulscher ME, Wollersheim H, Braspenning J, Kullberg BJ, van der Meer JW, Grol RP. Quality of antibiotic use for lower respiratory tract infections at hospitals: (how) can we measure it? Clin Infect Dis 2005;41:450–60.
42. Deschepper R, Van der Stickele R. De rol van culturele aspecten. Pharm Weekbl 2001;136:794–7.
43. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: A sociocultural perspective.Emerg Infect Dis 2002;8:1460–7.
44. Hofstede G. Allemaal anders denkenden: omgaan met cultuurverschillen. Amsterdam, Contact, 1991.
45. Grol R, Whitfield M, De Maeseneer J, Mokkink H. Attitudes to risk taking in medical decision making among British, Dutch and Belgian general practitioners. Br J Gen Pract 1990;40:134–6.
46. Kooiker S, van der Wijst L. Europeans and their medicines. Social and Cultural Planning Office of the Netherlands, 2003.
47. Goossens H, Peetermans W, Sion JP, Bossens M. 'Evidence-based' perioperative antibiotic prophylaxis policy in Belgian hospitals after a change in the reimbursement system. Ned Tijdschr Geneeskd 2001;145:1773–7.
48. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. Am J Med 1982;73:4–8.
49. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. JAMA 2002;287:612–7.
50. Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: Epidemiological study of randomised clinical trials published in the BMJ. BMJ 2002;325:24.
51. Coleman DL, Kazdin AE, Miller LA, Morrow JS, Udelsman R. Guidelines for interactions between clinical faculty and the pharmaceutical industry: One medical school's approach. Acad Med 2006;81:154–60.
52. Wetenschap op bestelling, Royal Netherlands Academy of Arts and Sciences, Amsterdam, 2005.

*This page intentionally blank*

# Chapter 3
# Cultural and Socioeconomic Determinants of Antibiotic Use

Stephan Harbarth and Dominique L. Monnet

Medicine is a social science in its very bone and marrow.

—Rudolf Virchow (1849)

## Background

Widespread antimicrobial resistance among bacterial pathogens has compromised traditional therapy with narrow-spectrum antibiotics and may result in adverse outcomes. Although no region in the world has been excluded from the inexorable spread of increasingly resistant bacteria, large disparities in the global epidemiology of antibiotic resistance can be observed.[1] The reasons for the uneven geographic distribution of antibiotic-resistant microorganisms are not fully understood. A variety of factors are responsible for this, but the selective pressure exerted by inappropriately used antibiotics is likely the most important.[2, 3] Antibiotic use may differ between and within countries. For example, in 2002, antibiotic consumption was three times higher in France than in the Netherlands, with other European countries reporting a wide range of antibiotic consumption rates between these extreme values.[4, 5]

Evaluating determinants leading to antibiotic overuse is a complex task. Cross-cultural comparisons may provide clues to its understanding, thus permitting policy makers to identify and implement those control measures that are most likely to be successful. In this chapter, we provide an overview of potential determinants influencing antibiotic use in different countries and present evidence that cultural and socioeconomic factors pervade all aspects of antibiotic use.

## Potential Determinants Explaining Disparities in Antibiotic Use

Why does antibiotic use vary so much across countries? Theoretically, five groups of determinants of the observed differences in the use of antimicrobial agents can be discerned (Table 3.1). These dimensions are derived from the concept that antibiotic use not only depends on clinical and microbiologic considerations and the frequency of infections but is also related to cultural and socioeconomic factors.[6–8]

TABLE 3.1. Determinants of differences in antibiotic use

| Dimensions | Determinants |
|---|---|
| Pathogen characteristics | Infection rates<br>Clonal dynamics<br>Transmissibility<br>Survival fitness and virulence of circulating strains |
| Physicians' antibiotic prescribing practices | Availability of diagnostic tests<br>Choice and dosing of antibiotic agents<br>Education and information about antibiotics<br>Peer pressure<br>Intensity and quality of industry promotion<br>Financial incentives |
| Antibiotic demand and patient characteristics | Perception of illness<br>Consumer attitudes and expectations<br>Educational level<br>Awareness about antibiotics (when they are active and about their ecologic effects)<br>Host susceptibility to disease |
| Cultural and socioeconomic factors | Day-care attendance and practices<br>Living conditions<br>Vaccination coverage<br>Social pressure |
| Healthcare and legal environment | Healthcare policy (e.g., reimbursement scheme)<br>Legal issues (e.g., malpractice laws)<br>Regulatory practices (e.g., over-the-counter dispensing) |

First, differences in pathogen characteristics, e.g., clonal dynamics, transmissibility, survival fitness, and virulence of circulating strains, may influence infection rates and need for treatment. For example, in Denmark, repeated outbreaks of *Mycoplasma pneumoniae* infections have triggered sharp, though short, increases in macrolide consumption.[9, 10] Second, physicians prescribing antibiotics may differ in their use, dosing, and choice of antibiotic agents. Third, characteristics of patient populations, consumer attitudes, and health-belief differences may influence the demand for antibiotics. Fourth, patients, as well as prescribers, are influenced by cultural and socioeconomic factors, e.g., child-care practices. Fifth, macro-level factors related to the healthcare environment may differ. Examples of these include legal issues, as well as regulatory healthcare policies that may influence antibiotic prescribing practices. In the following paragraphs, we will focus on the last three groups of explanatory determinants.

Additionally, we attempted to explain the large differences in antibiotic use observed among European countries by testing for statistical correlations between total antibiotic consumption and possible macro-level determinants of use (Table 3.2). Among those, the incidence of respiratory tract infections has been proposed as an explanatory factor. Although seasonal outbreaks caused by influenza have been responsible for year-to-year variations in single countries,[11] they represent an unlikely explanation for the large, but stable differences

TABLE 3.2. Determinants of antibiotic use and their relationship with total outpatient antibiotic use and over-the-counter use of antibiotics in the European Union

| Determinants | No. included European countries | Total outpatient antibiotic use (ATC group J01, DDD/1000 inh.-days, 1997)[47] Coefficient[f] | *p*-value | Over-the-counter use of antibiotics during the past year (% respondents, 2002)[48] Coefficient[f] | *p*-value |
|---|---|---|---|---|---|
| Incidence of infectious diseases | | | | | |
| Burden of respiratory tract infections (Disability-Adjusted Life Years per population), 2002[49] | 15 | 0.093 | >0.1 | 0.095 | >0.1 |
| Burden of chronic obstructive pulmonary disease (Disability-Adjusted Life Years per population), 2002[49] | 15 | −0.243 | >0.1 | −0.221 | >0.1 |
| Culture and perception of illness | | | | | |
| Uncertainty avoidance (index)[17 a, c] | 14 | 0.769 | 0.001 | 0.513 | 0.06 |
| Power distance (index)[17 b, c] | 14 | 0.746 | 0.002 | 0.300 | > 0.1 |
| Long-term orientation (index)[17 c] | 13 | −0.132 | >0.1 | −0.640 | 0.02 |
| Percent persons who rated their health as bad or very bad, 1996[50] | 15 | 0.449 | 0.09 | 0.578 | 0.02 |
| Education and knowledge about antibiotics | | | | | |
| Percent population who has completed at least upper secondary education, 1999[50] | 15 | −0.728 | 0.002 | −0.613 | 0.02 |
| Percent persons interviewed who considered as false the proposal: "Antibiotics kill viruses as well as bacteria", 2001[20] | 15 | −0.554 | 0.03 | −0.460 | 0.08 |
| Percent 15-year-old students who gave a correct answer for the diminishing activity of antibiotics, i.e., antibiotic resistance, 2000[25] | 15 | −0.604 | 0.02 | −0.527 | 0.04 |
| Socioeconomic factors | | | | | |
| Percent preschool-aged children taking up offers of preschool services, 1985–1996[51] | 11 | 0.661 | 0.03 | 0.263 | >0.1 |
| Percent women aged 25–49 years with at least one child aged 0–5 years who are employed, 1999[50] | 12 | −0.091 | >0.1 | −0.163 | >0.1 |
| Percent population aged 0–4 years[52] | 15 | −0.332 | >0.1 | −0.665 | 0.007 |
| Percent population aged 65 years and above[52] | 15 | 0.182 | >0.1 | 0.324 | >0.1 |
| Population density, 1997[52] | 15 | −0.136 | >0.1 | −0.040 | >0.1 |
| Percent population living in overcrowded households, 1996[50] | 15 | 0.599 | 0.02 | 0.581 | 0.02 |
| Percent infants breast-fed at 3 months of age, 1987–2000[53] | 15 | −0.513 | 0.05 | −0.014 | >0.1 |
| Percent infants vaccinated against *Haemophilus influenzae* type b, 1997[53] | 14 | −0.323 | >0.1 | −0.126 | >0.1 |

(*Continued*)

TABLE 3.2. (*Continued*)

| Determinants | No. included European countries | Total outpatient antibiotic use (ATC group J01, DDD/1000 inh.-days, 1997)[47] | | Over-the-counter use of antibiotics during the past year (% respondents, 2002)[48] | |
|---|---|---|---|---|---|
| | | Coefficient[f] | *p*-value | Coefficient[f] | *p*-value |
| Percent infants vaccinated against other childhood diseases (average of measles, mumps, rubella, and pertussis), 1997[53] | 15 | −0.036 | >0.1 | −0.038 | >0.1 |
| Healthcare system | | | | | |
| No. of physicians working in primary healthcare per population, 1997[53 d] | 14 | 0.622 | 0.02 | −0.271 | >0.1 |
| Patients must be registered with one general practitioner and change is limited, 1997[54] | 15 | −3.898[g] | 0.002 | −1.695[g] | >0.1 |
| Healthcare system responsiveness (index), 1999[55] | 15 | −0.509 | 0.05 | −0.727 | 0.002 |
| Percent persons very or fairly satisfied with their healthcare system, 1999[56] | 15 | −0.173 | >0.1 | −0.653 | 0.008 |
| Percent persons who never consulted a doctor, a dentist, or an optician during the past year, 1996[57] | 12 | 0.539 | 0.07 | 0.753 | 0.005 |
| Pharmaceutical market | | | | | |
| No. of inhabitants per public pharmacy, 1997[58] | 15 | −0.757 | 0.001 | −0.410 | >0.1 |
| No. of companies having at least one registered antibiotic, 1998[59 e] | 14 | 0.713 | 0.004 | 0.232 | >0.1 |
| No. of trade names of oral antibiotics (incl. brands and generics), 1998[59 e] | 14 | 0.763 | 0.002 | 0.611 | 0.02 |

[a] Uncertainty avoidance is a measure of tolerance to ambiguous situations which leads some individuals to feel more pressed for action than others.[17]

[b] Power distance is a measure of the interpersonal power or influence between two individuals when one is the subordinate of the other.[17]

[c] Other culture determinants as defined by Hofstede,[17] i.e., individualism and masculinity, showed no correlation.

[d] If general practitioners act as gatekeepers for access to specialists, number of general practitioners per population.

[e] Germany was an outlier and was excluded because of its very high number of companies having at least one registered antibiotic and number of brands or generic names of oral antibiotics.

[f] Two-tailed Spearman's coefficient.

[g] Independent-sample t-test for equality of means.

observed among European countries. Overall, we found no correlation between total antibiotic consumption and the burden represented by respiratory tract infections, and of chronic obstructive pulmonary disease (Table 3.2). Thus, it is unlikely that the incidence and pattern of other infectious diseases differ

substantially between these countries. Obviously, other factors explain the differences of antibiotic use among European countries and these will be examined in more details in the following paragraphs.

## The Cultural Perspective

Factors that influence antibiotic use include cultural conceptions, health beliefs, and patient demands. Cultural factors determine which signs and symptoms are perceived as abnormal and thus require medical care and antibiotic treatment.[12] Illness perception influences help-seeking behavior and clinical outcome.[13] For instance, transcultural differences in illness behavior were demonstrated in a survey among 2423 patients with tonsillitis in seven countries.[14] Multivariate analysis revealed that duration of illness was longest in former Socialist Eastern Europe because of sickness benefits, independent of patient and disease characteristics.

Cultural views of infectious conditions that require antibiotic treatment differ between countries.[15] Deschepper and co-investigators have contrasted labeling of disease and patients' attitude toward upper respiratory tract infections (URTI) in a Dutch and a Belgian city.[16] The Dutch participants labeled most URTI episodes as "common cold" or "flu." The Flemish participants labeled most of their URTI episodes as "bronchitis" and used more antibiotics. In general, participants with a Protestant background were more skeptical about antibiotics than those with a Catholic background. Likewise, antibiotic consumption in countries with predominantly Protestant populations is generally lower than those with predominantly Catholic populations.[2] However, this is not always true; notably Austria has an antibiotic consumption comparable to that of Germany.[5] This suggests that, although the main religious background is part of a country's culture, other factors may be better suited to describe the cultural influence.

According to Hofstede, a country's culture can be summarized by five determinants, i.e., uncertainty avoidance, power distance, individualism, masculinity, and long-term orientation.[17] A preliminary study by Deschepper and Vander Stichele showed that uncertainty avoidance and power distance, but not the three other culture determinants, were correlated with antibiotic consumption.[18] This was confirmed by our own data (Table 3.2). Uncertainty avoidance is defined as a measure of tolerance to ambiguous situations which leads some individuals to feel more pressed for action than others, whereas power distance is a measure of the interpersonal power or influence between two individuals when one is the subordinate of the other.[17] High uncertainty avoidance is likely to result in patient demand or physician prescription of antibiotics in situations where indication for treatment is unclear. Additionally, strong power distance between the prescriber and the patient or parent is likely to result in poor communication.

In previous cross-country comparisons looking at Germany, France, and the United States, we have suggested that cultural and behavioral characteristics of populations have a major impact on antibiotic prescribing practices at a national

level.[7, 8] Many American and French people seeking medical care because of cough and sputum production request to be treated by antibiotics; by contrast, most Germans consider such treatment as unnecessary overmedication. French patients have one of the highest antibiotic demand indices in Europe, as shown in a pan-European survey.[19] In that survey, France was the only European country where more than 50% of the interviewees expected an antibiotic for the treatment of "flu." The latter, however, probably reflects lack of knowledge that antibiotics are not active against viruses rather than a cultural difference[20] (Table 3.2). Conversely, acceptance of alternative medicine is high in Germany. Among 2111 Germans over 16 years of age, 83% had some sympathy for complementary medicine, whereas 40% disliked antibiotics because they could undermine natural immunity.[8]

As mentioned earlier, cultural factors influence the risk taking behavior of patients and physicians and their attitude toward a watchful waiting approach for febrile illness. One of the earliest reports that compared risk taking in medical decision making evaluated British, Dutch, and Belgian general practitioners.[21] Doctors in Belgium had the highest levels of "no risk-taking" attitudes with 60% preferring not to take risks; Dutch doctors had the lowest levels with only 24% preferring not to take risks. Not only physicians, but also patients of different origin may express variability in uncertainty avoidance, leading to different expectations of receiving antibiotics. In a survey from the United States, parents of Latino or Asian origin had the highest anxiety level compared to white parents when visiting a pediatrician for their sick child.[22]

We have recently performed a physician-based survey among Swiss pediatricians and showed that parental pressure for antibiotic prescription was less important in Switzerland than in a study from the United States.[23] Respectively, 96% (586/610) versus 67% (75/112, $p < 0.001$) of U.S. and Swiss pediatricians were asked by parents to prescribe antibiotics in the previous month; 48% (293/610) versus 13% (15/112, $p < 0.001$) reported that parents always or often pressured them to prescribe antibiotics. Thirty percent (183/610) of U.S. versus 14% (16/112, $p < 0.001$) of Swiss pediatricians occasionally or frequently complied with these requests.[24]

## The Socioeconomic Perspective

Misconceptions about antibiotic use and its ecologic consequences are common among the general public.[25] In 2000, the "Programme for International Student Assessment" (PISA) study, which assessed knowledge and skills attained by 265,000 adolescents in 32 countries, asked whether the use of antibiotics may lead to antibiotic resistance. Only 59% of students answered this question correctly. In 2001, a Eurobarometer survey showed that large variations existed among Europeans as per their knowledge that antibiotics were active against bacteria but not viruses.[20] A low level of understanding and knowledge about antibiotics is likely to influence usage of these drugs.

A Danish study[26] showed that children of mothers with only basic schooling were at highest risk of receiving multiple antibiotic prescriptions, whereas children of mothers with a high education or high household income had the lowest risk. A Spanish study confirmed the association between lower educational level and higher antibiotic use.[27] Among European countries, a higher percentage of the population having completed at least upper secondary education was associated with a lower antibiotic consumption (Table 3.2). However, these observations are not consistent with the findings of several other studies.[28, 29] For example, Hjern and colleagues from Sweden found that poor families had lower annual rates of antimicrobial drug use than did families with a higher socioeconomic status.[30, 31] These opposite findings from different Scandinavian countries show that the reciprocal relationship between socioeconomic status (including educational level) and antibiotic use is neither automatic nor universal and should not be generalized from one setting to another.[32]

Knowledge and education also influence auto-medication and compliance with antibiotic use, which vary tremendously between countries.[33, 34] Grigoryan and colleagues recently published a survey in 19 European countries, demonstrating that prevalence of self-medication with antibiotics varied from 1 to 210 per 1000; rates were highest in eastern and southern Europe.[34] In a global survey among 4088 participants,[35] prevalence of noncompliance with antibiotic prescriptions was highest in China (44%), Japan (34%), Mexico (26%), Philippines (26%) and Turkey (26%). According to this study, noncompliance not only depends on the country, but also on the age of the patient, antibiotic dosing and dispensing practice, and patient attitudes. Factors that had little influence on compliance were gender and educational level. Even well-educated patients may have a hard time complying. A respected U.S. physician revealed in an editorial[36]: "To be honest, I have a hard time finishing a 10-day course of antibiotics for bronchitis . . .."

Social constraints exert a strong effect on the use of antibiotic agents. This influence can be best illustrated by otitis media, the leading reason for excessive antimicrobial use in young children. Attendance at a child-care center outside the home correlates with an increased risk of otitis media and antibiotic use.[8] Therefore, differences in availability of and attendance to nonparental day-care facilities between countries lead to differing antibiotic prescription rates in young children. The need of parents to return to work and bring their children back to day care is an often underestimated pressure on antibiotic demand.

Besides day-care attendance of preschool children, other sociodemographic variables have been proposed as determinants of the frequency and volume of antibiotic use in a country, such as the proportion of preschool children and elderly, the average household size, and the overall population density.[37] Our own data, however, do not confirm these hypotheses (Table 3.2), which suggest that these factors do not play a major role in explaining country differences in antibiotic consumption, at least in Europe.

Last but not least, the frequency of breast-feeding, which is protective against lower and upper RTIs in early childhood,[38] can modify the incidence of pediatric infections and the need for antibiotic therapy. For instance, a population-based, longitudinal study from Canada has indicated that breast-feeding reduced the number of antibiotic treatments given to children entering day care before 2.5 years of age.[29] This study also showed that children could be protected by being taken care of in a familial setting.

## The Health Economic and Regulatory Perspective

Ecologic evidence, at both the cross-country and within-country levels, suggests that antibiotic use is affected by reimbursement policies, financial incentives, healthcare regulation, and marketing strategies of the pharmaceutical industry.[39] For instance, countries with a competitive healthcare market and a great diversity of antibiotic trade names have a higher antibiotic consumption.[40] This may be one of the strongest factors to explain variations of antibiotic consumption among European countries (Table 3.2). A high number of antibiotic trade names, thus a high level of competition between pharmaceutical companies, probably necessitates increased promotional activities towards prescribers. In a French study, general practitioners meeting with more than 10 pharmaceutical representatives per month had a higher rate of antibiotic prescription for acute rhinopharyngitis.[41]

Likewise, countries or regions with a high density of medical practices and pharmacies tend to have higher antibiotic prescription rates[42, 43] (Table 3.2). Additionally, European countries where patients must register with one family physician have a significantly lower antibiotic consumption compared to countries where the choice of physician is free (Table 3.2). In Hungary, regional differences in antibiotic consumption were explained by the proportion of population benefiting from the "public medicine service" and therefore having free access to medicines.[44] Other examples of the effects of healthcare regulation are the decreased use of antibiotics after interdiction of over-the-counter sales of antimicrobial agents in Chile and the regulatory restriction of perioperative antibiotic prophylaxis in Belgium.[39] In Denmark, the excessive use of tetracyclines, mainly for RTIs, was corrected by delisting tetracyclines, i.e., removing them from the list of subsidized medicines, which resulted in a decrease in tetracycline use and was followed by a parallel decrease in tetracycline resistance among different bacteria.[9] Likewise, the delisting of fluoroquinolones resulted in a temporary drop in the consumption of this class of antibiotics. All these are examples of financial disincentives that have shown their effectiveness in changing physicians' prescribing patterns and choice of antibiotic agents.

The most extreme example of "induced demand" produced by financial incentives is illustrated by healthcare providers in several Asian countries who can earn a significant proportion of their income from dispensing drugs. In contrast to Europe and the United States, separation of dispensing and prescribing is not a well-established system in these countries, in which healthcare

providers have compensated for relatively low medical service revenue by prescribing a high volume of broad-spectrum antimicrobial agents.[45] This illustrates how financial incentives linked to the pharmaceutical reimbursement system and physician–industry interactions can strongly influence antibiotic prescribing. Since hospitals and physicians rely heavily on profits from drug price differences as a source of revenue, little progress had been made in most Asian countries in promoting a separation of dispensing and prescribing. A notable exception is South Korea, where, against the opposition of physicians and the pharmaceutical industry, a policy introduced in 2000 prohibited physicians from dispensing drugs and pharmacists from prescribing drugs.[46] This new policy decreased overall prescribing of antimicrobial agents and selectively reduced inappropriate prescribing for viral infections.

## Summary

Effects exerted at the macro-level by the sociocultural and economic environment contribute substantially to the observed differences in antibiotic prescribing practices. Consequently, failure to understand the sociocultural and economic perspectives of antibiotic use will lead to inadequate conclusions about the chances of success for possible interventions. More research to inform decision-makers on the macro-level determinants of the variation in antibiotic use and resistance patterns is urgently needed.

## *References*

1. Tiemersma EW, Bronzwaer SL, Lyytikainen O, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. Emerg Infect Dis 2004;10:1627–34.
2. Baquero F, Baquero-Artigao G, Canton R, Garcia-Rey C. Antibiotic consumption and resistance selection in *Streptococcus pneumoniae.* J Antimicrob Chemother 2002;50 Suppl S2:27–37.
3. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes.* Emerg Infect Dis 2004;10:514–7.
4. Bjerrum L, Boada A, Cots JM, et al. Respiratory tract infections in general practice: Considerable differences in prescribing habits between general practitioners in Denmark and Spain. Eur J Clin Pharmacol 2004;60:23–8.
5. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. Lancet 2005;365:579–87.
6. Avorn J, Solomon DH. Cultural and economic factors that (mis)shape antibiotic use: the nonpharmacologic basis of therapeutics. Ann Intern Med 2000;133:128–35.
7. Harbarth S, Albrich W, Goldmann DA, Huebner J. Control of multiply resistant cocci: Do international comparisons help? Lancet Infect Dis 2001;1:251–61.
8. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: A sociocultural perspective. Emerg Infect Dis 2002;8:1460–7.

9. DANMAP 1999—Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. Copenhagen, Statens Serum Institut, 2000.
10. DANMAP 2005—Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark. Copenhagen, Statens Serum Institut, 2006.
11. Bauraind I, Lopez-Lozano JM, Beyaert A, et al. Association between antibiotic sales and public campaigns for their appropriate use. JAMA 2004;292:2468–70.
12. Kleinman A, Eisenberg L, Good B. Culture, illness, and care: Clinical lessons from anthropologic and cross-cultural research. Ann Intern Med 1978;88:251–8.
13. Alberts JF, Sanderman R, Gerstenbluth I, van den Heuvel WJ. Sociocultural variations in help-seeking behavior for everyday symptoms and chronic disorders. Health Policy 1998;44:57–72.
14. de Melker RA, Touw-Otten FW, Kuyvenhoven MM. Transcultural differences in illness behaviour and clinical outcome: an underestimated aspect of general practice? Fam Pract 1997;14:472–7.
15. Pechere JC, Cenedese C, Muller O, et al. Attitudinal classification of patients receiving antibiotic treatment for mild respiratory tract infections. Int J Antimicrob Agents 2002;20:399–406.
16. Deschepper R, Vander Stichele RH, Haaijer-Ruskamp FM. Cross-cultural differences in lay attitudes and utilisation of antibiotics in a Belgian and a Dutch city. Patient Educ Couns 2002;48:161–9.
17. Hofstede GH. Culture's Consequences: Comparing Values, Behaviors, Institutions and Organizations across Nations, ed 2. Thousands Oaks, CA, Sage, 2001.
18. Deschepper R, Vander Stichele RH. Uiteenlopend antibioticagebruik in Europa: de rol van culturele aspecten. Pharm Weekb 2001;136:794–97.
19. Branthwaite A, Pechere JC. Pan-European survey of patients' attitudes to antibiotics and antibiotic use. J Int Med Res 1996;24:229–38.
20. European Commission. Eurobarometer 55.2. Europeans, Science and Technology. Directorate-General of Research, Brussels, European Commission, 2001.
21. Grol R, Whitfield M, De Maeseneer J, Mokkink H. Attitudes to risk taking in medical decision making among British, Dutch and Belgian general practitioners. Br J Gen Pract 1990;40:134–6.
22. Mangione-Smith R, Elliott MN, Stivers T, McDonald L, Heritage J, McGlynn EA. Racial/ethnic variation in parent expectations for antibiotics: Implications for public health campaigns. Pediatrics 2004;113:e385–94.
23. Bauchner H, Pelton SI, Klein JO. Parents, physicians, and antibiotic use. Pediatrics 1999;103:395–401.
24. Egger M, Harbarth S, Gervaix A. Differences in antibiotic prescribing patterns between Swiss and US pediatricians. 24th Annual ESPID Meeting, Basel, 2006 (abstract O3).
25. Harbarth S, Albrich W, Pittet D. Semmelweis' legacy: Insights from an international survey among 265,000 students in 32 countries. Int J Hyg Environ Health 2004;207:481–5.
26. Thrane N, Olesen C, Schonheyder HC, Sorensen HT. Socioeconomic factors and prescription of antibiotics in 0- to 2-year-old Danish children. J Antimicrob Chemother 2003;51:683–9.
27. Garcia-Rey C, Fenoll A, Aguilar L, Casal J. Effect of social and climatological factors on antimicrobial use and *Streptococcus pneumoniae* resistance in different provinces in Spain. J Antimicrob Chemother 2004;54:465–71.

28. Henricson K, Melander E, Molstad S, et al. Intra-urban variation of antibiotic utilization in children: Influence of socio-economic factors. Eur J Clin Pharmacol 1998;54:653–7.
29. Dubois L, Girard M. Breast-feeding, day-care attendance and the frequency of antibiotic treatments from 1.5 to 5 years: A population-based longitudinal study in Canada. Soc Sci Med 2005;60:2035–44.
30. Hjern A, Haglund B, Rasmussen F, Rosen M. Socio-economic differences in daycare arrangements and use of medical care and antibiotics in Swedish preschool children. Acta Paediatr 2000;89:1250–6.
31. Hjern A, Haglund B, Rosen M. Socioeconomic differences in use of medical care and antibiotics among schoolchildren in Sweden. Eur J Public Health 2001;11:280–3.
32. Melander E, Nissen A, Henricson K, et al. Utilisation of antibiotics in young children: Opposite relationships to adult educational levels in Danish and Swedish counties. Eur J Clin Pharmacol 2003;59:331–5.
33. Pechere JC. Patients' interviews and misuse of antibiotics. Clin Infect Dis 2001;33 Suppl 3:S170–3.
34. Grigoryan L, Haaijer-Ruskamp FM, Burgerhof JG, et al. Self-medication with antimicrobial drugs in Europe. Emerg Infect Dis 2006;12:452–9.
35. Pechere JC, Hughes D, Kardas P, Cornaglia G. Non-compliance with antibiotic therapy for acute community infections: a global survey. Int J Antimicrob Agents 2007;29(3): 245–53.
36. Daley J. Medical uncertainty and practice variation get personal: What should I do about hormone replacement therapy? Ann Intern Med 1999;130:602–4.
37. Bruinsma N, Hutchinson JM, van den Bogaard AE, Giamarellou H, Degener J, Stobberingh EE. Influence of population density on antibiotic resistance. J Antimicrob Chemother 2003;51:385–90.
38. Wilson AC, Forsyth JS, Greene SA, Irvine L, Hau C, Howie PW. Relation of infant diet to childhood health: Seven-year follow up of cohort of children in Dundee infant feeding study. BMJ 1998;316:21–5.
39. Harbarth S, Samore MH. Antimicrobial resistance determinants and future control. Emerg Infect Dis 2005;11:794–801.
40. Monnet DL, Ferech M, Frimodt-Moller N, Goossens H. The more antibacterial trade names, the more consumption of antibacterials: A European study. Clin Infect Dis 2005;41:114–7.
41. Mousqués J, Renaud T, Scemama O. Variabilité des pratiques médicales en médecine générale: la prescription des antibiotiques dans la rhinopharyngite aiguë. Questions d'Economie de la Santé 2003;70:1–8.
42. Llor C, Bjerrum L. Background for different use of antibiotics in different countries. Clin Infect Dis 2005;40:333.
43. Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: Evidence from Switzerland. Health Policy 2005.
44. Matuz M, Benko R, Doro P, et al. Regional variations in community consumption of antibiotics in Hungary, 1996–2003. Br J Clin Pharmacol 2006;61:96–100.
45. Harbarth S, Oberlander C. Do health care regulation and physician–industry interaction influence antibiotic resistance rates? The example of antimicrobial prescribing and dispensing in Japan. International Conference on Improved Use of Medicine. Chiang Mai, Thailand, WHO, March 2004 (abstract 391).

46. Park S, Soumerai SB, Adams AS, Finkelstein JA, Jang S, Ross-Degnan D. Antibiotic use following a Korean national policy to prohibit medication dispensing by physicians. Health Policy Plan 2005;20:302–9.
47. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851–3.
48. European Commission. Eurobarometer 58.2. Antibiotics. European Opinion Research Group. Brussels, Belgium, European Commission, Health and Consumer Protection Directorate-General, 2003.
49. WHO. Death and DALY estimates for 2002 by cause for WHO Member States. WHO, 2002.
50. European Commission. Living conditions in Europe, statistical pocketbook. In: European Commission, Luxembourg, 2000.
51. Danish Government. Structural monitoring—International benchmarking of Denmark. Copenhagen, Danish Government, 2002.
52. U.S. Bureau of Census. International Data Base—Aggregations. Bureau of the Census, 2005.
53. WHO. European health for all database. World Health Organization Regional Office for Europe, 2003.
54. WHO Regional Office for Europe. Highlights on health, 1996–1999. World Health Organization Regional Office for Europe, 2002.
55. Navarro V. Assessment of the World Health Report 2000. Lancet 2000;356:1598–601.
56. The social situation in the European Union 2001. Eurostat Luxembourg, 2001.
57. Office for Official Publications of the European Communities. Key data on Health 2000, Data 1985–1995. Edition 1999.
58. Groupement International de la Répartition Pharmaceutique Européenne. European pharmaceutical distribution data 1997. IMS Health, 1998.
59. European Commission. Pharmaceutical prices database. Medicinal products for human use marketed in the European Union In: European Commission, Pharmaceuticals and Cosmetics, ed. Brussels, Belgium, European Commission, 1998.

# Chapter 4
# Electronic Prescribing

Mical Paul, Roberto Cauda, and Leonard Leibovici[1]

## Foreword

Prescription of antibiotic treatment is complex. While most patients with fever do not require antibiotic treatment, early administration of appropriate antibiotics to patients with certain bacterial infections improves survival. Antibiotic use leads to bacterial resistance. Antibiotics can thus be justified only when truly needed. The narrowest spectrum antibiotic should be used to prevent resistance development to the more advanced antibiotics. However, the pathogen(s) causing infections become known only after 24–72 hours of infection onset and at many times are not isolated at all.

Computerized decision support systems are an attractive means of improving antibiotic treatment. The data necessary for prescribing antibiotics are quantitative: local epidemiology of infections; local resistance patterns; costs, adverse events, and induction of resistance for different antibiotics; results of *in vitro* susceptibility testing. Physicians cannot be expected to command these data, particularly as they change in time. The process of combining the data to a single decision for antibiotic prescription entails multiplication of large matrices. Again the physicians cannot be expected to perform this multiplication. They probably use heuristics, simplified rules, to reduce the dimensions of the problem. The result is less than optimal. Inappropriate empirical antibiotic treatment is prescribed to 30–50% of patients.[1–10] Superfluous and unnecessary antibiotic treatment is probably more frequent. Patients given inappropriate treatment die twice as often as patients given appropriate treatment.[1–10] Superfluous antibiotic treatment has contributed to the development of bacterial species resistant to all available antibiotics.

In the following chapter we present the rationale for computerized decision support for antibiotic prescription; the experience gained thus far; the lessons learned from previous experience and future directions in electronic prescribing. We will focus on the treatment of bacterial infections. In practice, antibiotic decision-making is much more complex, involving the prevention of infections using prophylaxis and treatment of viral, parasitic, fungal, and other infectious agents.

## Antibiotic Decision-Making

The process of prescribing antibiotic treatment is more complex than prescription of any other drug or intervention in medicine. It affects not only the patient at the time of prescription, but also the patient's future with regard to infections, the possibility to treat them, and future patients. Prescription of a last resort drug to one patient might mean no antibiotic treatment for the next patient. Alternatively, withholding antibiotic treatment from one patient might mean cure for another.

Analysis of the decision-making process demonstrates its complexity and the place for electronic prescription. We will present the crossroads of this process.

**1. Does this patient need antibiotic treatment?**

The first question is the most difficult. We will break this question further:

a. Does this patient have a bacterial infection?
b. What is the site of infection?
c. Is there evidence warranting antibiotic treatment for this site of infection?

Determining whether the patient has a bacterial infection entails history taking, physical examination, and additional testing such as radiology, microbiology and other specific tests. The physician should know the predictive value of each piece of information obtained. For example, does the fact that the patient reports true rigors accompanying the fever increase the probability of bacterial infection? Does a normal leukocyte count with an increased percentage of neutrophils predict bacterial infection?

Determining the site of infection necessitates similar data and further interpretation. Is the risk for soft-tissue infection increased in a diabetic patient? Are rigors more common in urinary tract infections than in pneumonia?

Antibiotic treatment is indicated for certain bacterial infections but not for others. We will treat a patient with cystitis[11] but usually should not treat a patient with asymptomatic bacteriuria.[12] For some infections, early treatment can be safely deferred until appropriate microbiological samples are obtained (e.g., endocarditis) but not for others (e.g., bacterial meningitis). A close inspection of question 1c will reveal that the question is incomplete. What outcome are we looking at when asking whether antibiotic treatment is indicated? By using antibiotic treatment we aim to increase survival, prevent further morbidity, and alleviate acute suffering. However, antibiotic treatment is largely given with no evidence for benefit with regard to survival, serious morbidity, or symptoms. The type of benefit afforded by antibiotics and its extent dictate the necessity for treatment.

**2. Which antibiotic(s) treatment?**

Again this is a very broad question, which must be divided into its components:

a. What are the likely bacteria causing this infection?
b. What is the susceptibility of these bacteria to antibiotics, currently, at my locale?
c. Is there an advantage or a disadvantage to one class of antibiotics over another?

The bacterial spectrum will be dictated by the patient's background, the likely site of infection, the place where the infection was acquired, and specific circumstances. An impressive amount of knowledge is needed to answer question 2a. Certain diseases may predispose patients to specific infections and pathogens. A prosthetic heart valve or any prosthetic device may predispose patients to staphylococcal infections. Cancer patients with neutropenia are at risk for certain Gram-positive infections and *Pseudomonas aeruginosa*. Physicians should be well acquainted with the bacterial spectrum of specific sites of infection, such as urinary tract infection or pneumonia. However, causation may be influenced by underlying conditions and specific circumstances. The pathogens causing urinary tract infection in an elderly male with a urinary catheter differ from those causing the same infection in young women. Bacteria infecting intravenous catheters differ with or without parenteral nutrition. A major factor affecting the bacterial spectrum of a specific site of infection is its place of acquisition. Thus, community-acquired pneumonia is caused by different bacteria than hospital-acquired pneumonia, while the circumstances surrounding ventilator-associated pneumonia virtually separate it into a different entity.

Knowledge regarding the local susceptibilities of bacteria to antibiotics is required to prescribe antibiotics. Susceptibilities differ in different countries, between the community and the hospital within the same country, and even between different regions in the same hospital. Temporary outbreaks of resistant bacteria, such as vancomycin-resistant enterococci or carbapenem-resistant *Acinetobacter baumannii*, may affect local epidemiology. Physicians' acquaintance with these data is quite vague. It is likely that the clinician reading this chapter is unaware of the susceptibility of *Escherichia coli* species to ceftriaxone in his/her locale.

Finally, the mechanism of action, pharmacokinetic and pharmacodynamic properties of the antibiotic drugs must be taken into account. The ability of aminoglycosides to penetrate bacteria is reduced in an anaerobic environment and low external pH. Thus, aminoglycosides would be an inadequate choice to treat Gram-negative bacteria causing diabetic foot infections. Pharmacokinetics relate to the absorption, tissue distribution, metabolism, and elimination of drugs. An antibiotic with good lung penetration is preferable for the treatment of pneumonia. Pharmacodynamics describe the relationship between drug concentrations and effects. Certain antibiotics are bacteriostatic in the sense that blood and tissue concentrations achieved using usual doses result in bacterial inhibition but not killing. A bacteriostatic antibiotic may suffice for the treatment of pneumonia but will be inadequate to treat endocarditis. Question 2c is considered at the empirical stage, but also when the causative bacteria and their susceptibilities to antibiotics are known. The culprit pathogen may be susceptible to both clindamycin and cloxacillin, but clindamycin may be inadequate since it is bacteriostatic.

**3. Can this antibiotic be administered to my patient and at what dose?**

As with any drug, hypersensitivity to specific drugs must be considered. Hypersensitivity cross-reactivity within antibiotic classes should be considered.

Other contraindications, such as renal failure or liver dysfunction, must be considered when selecting the agent. Finally the dose used should be adjusted to its clearance.

Clearly, the knowledge required to select antibiotic treatment is far beyond that easily available to the physician at the time of antibiotic prescription. The matrices involved cannot be calculated by the physician alone in real time. Therefore, in practice, physicians rely on simple rule-based algorithms, recommendations, and guidelines. These guidelines attempt to group patients and risk factors and use general evidence to recommend specific antibiotic treatment. The results achieved by this technique are suboptimal. It is interesting to observe that empirical antibiotic(s) are uniformly inappropriate (e.g., empirical treatment does not provide coverage of subsequently isolated pathogens) in about 30% of patients in different countries and different settings.[1–10] This occurs in countries where antibiotic resistance is minimal and *Escherichia coli* can be treated with ampicillin[2, 10] and in countries with substantial resistance problems where a large percentage of *E. coli* species in the community are resistant to quinolones.[5–7] It occurs with community-acquired infections[2, 6–8] and in the intensive care unit.[1, 3, 4, 8, 9] There seems to be a performance limit to the heuristic or "guideline-based" approach, which has been repeatedly shown. This is important, because inappropriate empirical antibiotic treatment is associated with increased mortality in severe infections, independent of other risk factors for death. Independent increases in mortality range from 1.4- to 6-fold in different series and among patients with different risks.[1–10]

The other coin of suboptimal antibiotic treatment is resistance induction. The rate of unnecessary and superfluous antibiotic treatment has not been systematically assessed in most series. It is probably of a larger magnitude than that of inappropriate antibiotic treatment. Superfluous antibiotic treatment contributes to the increasing problem of resistant bacteria.

## The Place for Electronic Antibiotic Prescribing

Computer systems are an attractive solution to the problems encountered with antibiotic prescribing. Following the analysis of the process leading to antibiotic prescription, computer assistance may be useful at several points along this process. We will try to identify these points below.

### *Assembling Patients' Data*

The variables needed to prescribe antibiotics pertain to the patient's medical history, laboratory results, current and former microbiological samples, and more. Nowadays, and increasingly in the future, these data will be available electronically. For example, the finding that a patient has undergone a urological procedure 2 weeks before presentation with a urinary tract infection will influence the bacterial spectrum and thus the antibiotic chosen. Another patient might have had

a urine culture obtained 3 days before presenting to the hospital with pyelonephritis. Results of the culture will dictate the appropriate treatment for this patient. These data should be transferred electronically to the physician at the time of antibiotic prescription.

## *Use of Local Data*

This last scenario is rare. Most commonly the physician will not have relevant culture results at the time of initial antibiotic prescription. However, the databases in the microbiological laboratory contain similar data obtained from former patients. Any laboratory should be able to enlist the bacteria it has recently identified by source (e.g., urine, blood) and their susceptibilities to antibiotics. These data can be used to predict the bacterial spectrum of the current infection and/or bacterial susceptibility to antibiotics. The more structured the local databases, the more information can be gained. Thus, if registry of place of infection acquisition and previous antibiotic use is kept with each isolate, the degree of matching for the next patient is expected to improve. Computer systems can assemble previously available local microbiological data to predict the cause of subsequent infections and their antibiotic susceptibilities.

## *Computation of Large Matrices*

Computers can assist with computation of large probabilistic matrices. At the time of empirical antibiotic treatment the matrices are huge, since no definitive data are usually available. The matrices consist of the probability for bacterial infection, probability for the different sites of infection, probabilities for causative bacteria, and the susceptibilities of all bacteria to all antibiotic regimens. As more data become available, the matrices become smaller. For example, when preliminary results of blood cultures with growth and morphology become known, the spectrum of bacteria considered is restricted. At any stage, computational assistance may aid clinicians.

## *Bringing Evidence-Based Medicine to Clinicians*

The final decision must be based on evidence showing benefit to the treatment administered. Electronic systems can bring the evidence to the physician's workstation, in real time. Preferably the information should be structured in a way that will help the physician to answer his/her question simply, at a requested level of detail, stating the degree of evidence supporting the answer. For example, should beta-lactam monotherapy be used or is the combination of a beta-lactam with an aminoglycoside treatment advantageous for a patient with febrile neutropenia? A structured way of presenting available evidence to the physician would begin with the briefest and highest level of evidence available, for example an abstract of a systematic review of randomized controlled trials from the Cochrane Library.[13] The next level of detail would be the complete systematic review and

then individual relevant randomized trials. In a different example, a physician might ask whether early valve replacement will improve the outcome of a patient with *Staphylococcus aureus* endocarditis. In this case the briefest answer might be found in a narrative review and evidence can be shown in more detail from prospective and then retrospective observational studies.

### *Pattern Recognition Alerts*

At many stages, antibiotic prescription is influenced by the local epidemiology. Electronic surveillance in the microbiology lab can serve to detect outbreaks of specific organisms in a specific unit, or an emerging resistance trait. This knowledge can serve mainly for prevention but also for appropriate treatment.

### *"Watchdog" Alerts*

Simple alerts at the level of antibiotic prescription can prevent prescription errors.[14, 15] Prescription of a beta-lactam to a patient with hypersensitivity to penicillin, prescription of a macrolide to a patient treated with warfarin, aminoglycoside in an inappropriate high dose for a patient with renal failure—all should trigger a warning not to prescribe, to adjust antibiotic dosing, to adjust the dosing of other medications, etc.

### *Reinforcement of Guidelines*

At another level, if a decision is made to reinforce local guidelines, the physician's workstation is an attractive place to intervene. Matching diagnoses with recommendations, presenting the guidelines in a user-friendly format, or forbidding the prescription of antibiotics that are not recommended—several electronic techniques can be used to improve adherence to local guidelines.

## Testing of Antibiotic Decision Support Systems

Development of a decision support system for antibiotic treatment is not merely sufficient. Interventions in medicine should be tested. Analogous to the evaluation of a new drug, a computerized system should progress through phases assessing its safety and efficacy. We should first test the content of the system: does it perform as expected given data on real patients? Randomized controlled trials have become the gold standard for the assessment of interventions in medicine. Thus, ultimately computerized systems should be evaluated for efficacy and safety in randomized trials.

Testing an electronic system in a randomized controlled trial is not straightforward. Computerized decision support systems are complex interventions. The methods commonly used for testing interventions in medicine are not well adapted for these interventions. It is probably impossible, for example, to design a double-blinded controlled trial for the testing of a medical decision support

system. A generally accepted methodology for testing has not been developed yet. We will highlight several problems relevant to such testing.

## *Who Should Be Randomized?*

Decision support systems tend to educate their users. Conventional randomization of patients would result in underestimation of the system's effect. For example, a physician advised by an electronic system that ampicillin plus macrolide is the preferred local treatment for community-acquired pneumonia might prescribe the same treatment for his/her next patient with pneumonia. Thus, either physicians or units should be randomized, a design termed *cluster randomization*.

The use of units for randomization (e.g., hospital, ward, clinic) may be advantageous with regard to interventions involving antibiotic treatment. Antibiotic use influences the environment and the ecology of the unit. Changes in antibiotic prescription for one patient may affect the outcomes of another. For example, excessive use of cephalosporins in the unit may trigger an outbreak of pseudomembranous colitis that will affect other hospitalized patients who have not received antibiotics. Alternatively, restriction of antibiotic use may prevent transmission of highly resistant bacteria. Cluster randomization by units allows for the complete assessment of an intervention involving antibiotic use.

Cluster randomization has its own drawbacks. The main one is that the differences measured may be caused by different baseline practices in the clusters and not by the intervention. In addition, clustering reduces the effective sample size and should be taken into account when analyzing the results of such trials with appropriate statistical methods.

## *What Are the Outcomes We Should Measure?*

An intervention to improve antibiotic treatment should be aimed at improving mortality, morbidity, use of antibiotics with an adverse ecological impact or at reducing costs. If the main target is to reduce use of antibiotics or costs, we should show that mortality and morbidity were not affected. However, trials powered to detect a difference (or equivalence) in mortality among inpatients with moderate to severe infections will demand an enormous sample size. A convenient proxy outcome is matching the *in vitro* susceptibility of the isolated pathogen(s), as a large amount of data links it to improved survival.[1–10] Yet the pathogen of infection will be known only in about a third of patients with severe infections.

## *Differentiating between the System's Performance and User Interactions*

Necessarily, the system's effect will depend on users' interaction with it. A system might perform perfectly, but if not used will have no effect. Interaction with the system is complex. It should be rapid enough to use in real time, should be user-friendly, and should probably provide the physician with some incentive for

its use. Double data entry should be avoided. The system's advice should be clear. Intrinsic and overall performance should be assessed separately, but ultimately the success of the system will depend on both.

### *External Validity*

External validity refers to the extent to which the results of a study provide a correct basis for generalization to other circumstances. Interventions involving antibiotic use are not only location-dependent, but also time-dependent. Adjustment to local epidemiology and resistance patterns is mandatory. Even after adjusting, a system that has been shown to successfully restrict antibiotic use in an intensive care unit in Spain, will most probably perform poorly in Denmark. Without adjustment to the local formulary a system developed in one hospital will be useless in a different hospital. A decision support system for antibiotic prescription must obviously include mechanisms for local and temporal calibration. The external validity of trials assessing decision support for antibiotic prescription should be carefully assessed.

### *Ethical Considerations*

The ethics of antibiotic prescription are complex. Is it ethical to prescribe less than the broadest spectrum antibiotic to a severely septic patient? Is it ethical to provide the broadest spectrum antibiotic? Is it ethical to withhold antibiotic treatment from a comatose patient with very poor prognosis? Is it ethical to treat this patient? Is it ethical to launch a community-based campaign to limit antibiotic use? Many times these questions are addressed implicitly and locally. During a trial, offering patients participation and asking for their consent will transform the dilemmas to explicit ones.

## Existing Experience: Review of the Literature

Despite the revolution in computer systems in recent decades, surprisingly few medical computerized decision support systems have reached the testing phase and much fewer have entered clinical use. To examine existing experience in light of the issues previously discussed we performed a review of the literature. The objectives of our review were to assess the types of decision support systems developed and tested; the design of the trials assessing these systems; the types of outcomes assessed in these trials; and the effect of decision support systems on antibiotic treatment and patient-related outcomes.

### *Methods*

#### Types of Studies

For the purposes of our review, we defined a decision support system as any electronic system in which characteristics of individual patients are used to generate patient-specific recommendations.[16] A decision support system for antibiotic

treatment was defined as any decision support system that provided a specific recommendation regarding either type or dose of antibiotic prophylaxis or treatment. Systems that provided general guidelines or recommendations of antibiotic treatment and/or prophylaxis were not included.

We included any study assessing the performance or impact of an antibiotic decision support system. We classified the trials by their design:

- Randomized controlled trials
- Comparative nonrandomized trials
- Noncomparative trials with gold standard outcome measure (*in vitro* testing, drug levels)
- Noncomparative studies without gold standard outcome measure (assessed against expert opinion, clinician's performance, etc.)

In addition, we recorded whether the nonrandomized studies were prospective or retrospective, and if prospective, whether interventional or noninterventional.

### Types of Outcome Measures

We extracted outcome data as reported in the studies. We also classified the outcomes assessed to:

- Patient-related end outcome: results of the intervention that are directly related to patient morbidity or mortality (e.g., mortality, fever duration, hospitalization duration, etc.)
- Non-patient-related end outcomes: results of the intervention that are not directly related to patient morbidity or mortality (e.g., antibiotic costs)
- Intermediary outcomes: any other outcome (e.g., appropriate antibiotic treatment as defined in study, appropriate antibiotic dosing, achieving adequate drug blood levels, etc.)

### Search Strategy

We searched PUBMED 1966 to October 2006 using the following terms and their medical subject headings [MESH]: "Computer Systems"[MeSH] OR "Therapy, Computer-Assisted"[MeSH] OR "Drug Therapy, Computer-Assisted"[MeSH] OR "Diagnosis, Computer-Assisted"[MeSH] OR "Decision Making, Computer-Assisted"[MeSH] OR "Computer-Assisted Instruction"[MeSH] OR "Medical Informatics"[MeSH] OR "Decision Support Systems, Clinical"[MeSH] OR "Decision Support Systems, Management"[MeSH] OR "Decision Making, Computer-Assisted"[MeSH] OR "Decision Support Systems, Clinical"[MeSH] OR "Decision Support Systems, Management"[MeSH] OR "Neural Networks (Computer)"[MeSH] OR "Integrated Advanced Information Management Systems"[MeSH] OR "Informatics"[MeSH] OR "Information Systems"[MeSH] OR "Hospital Information Systems"[MeSH] OR "Reminder Systems"[MeSH] OR "Artificial Intelligence"[MeSH]) AND antibiotic*. We also searched the web for antibiotic systems at:www.openclinical.org/dssevalstudies.html,

www.informatics-review.com/decision-support/, http://clinicaltrials.gov/ct/gui, and http://www.controlled-trials.com. References of systematic reviews of medical computerized systems or interventions to improve antibiotic prescribing were scanned for further publications.[17–19] We selected reports including assessment or testing of the system from this search strategy.

### Data Extraction

In addition to study design and outcomes, we extracted from each study the following data:

- Study years
- Location developed and location tested
- Study settings (community, hospital, intensive care unit [ICU])
- Logical core of the decision support system (e.g., rule-based, neural network, causal probabilistic network)
- Whether antibiotics' ecological impact was explicitly taken into account

We tried to assess from the primary or further publications whether the system entered routine clinical use.

## *Results*

We identified 71 potentially relevant publications from the search. Of these, 22 reports did not fulfill the definition of a decision support system: the system did not use patient-specific variables in 13 reports or did not generate patient-specific recommendations in 10. Twelve reports described antibiotic decision support systems that have been developed but were not tested. Thirty-eight publications described and assessed 14 different antibiotic decision support systems, which form the basis of our analysis.

### Antibiotic Selection Systems

Seven decision support systems were designed to support the selection of antibiotic treatment (Table 4.1). Four systems provided recommendations only regarding the type of antibiotic/(s),[20–23, 43] while three provided also a dosing recommendation.[24–42, 44–46] A single system provided recommendations that included no antibiotic treatment (the HELP system).[24–40] Two systems attributed an explicit ecological value to antibiotics.[23, 43] These systems ranked antibiotics by their presumed adverse ecological impact and included this rank in their selection of the antibiotic regimen.

Five decision support systems were assessed in clinical trials. Two were tested in noncomparative, noninterventional studies.[11, 43] Leibovici et al. assessed the performance of a rule-based system in a prospective cohort of inpatients against *in vitro* susceptibilities of clinically significant isolated bacteria.[23] Mullett et al. similarly assessed a system based on case based reasoning in a retrospective cohort of inpatients.[43] By definition of the noninterventional design, both studies

TABLE 4.1. Antibiotic computerized decision support systems providing advice on antibiotic selection

| Reference | Type of recommendation | Location developed | Location tested | Logical core | Eco[a] values | Year(s) tested | Setting | Trial design | Types of outcomes assessed | Specific outcomes | Systems' effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Yu 1979[20–22] "MYCIN" | Type of antibiotic | USA | No clinical testing | Rule-based | No | 1979 | No clinical testing | Non comparative non interventional. Assessment against physicians' opinions | Intermediary | 1. Appropriate antibiotic treatment | 1. Improved |
| Leibovici 1997[23] | Type of antibiotic | Israel | Same as developed | Rule-based | Yes | 1997 | Hospital | Non comparative non interventional, prospective. Assessment against *in vitro* susceptibilities | Intermediary | 1. Appropriate antibiotic treatment | 1. Significantly Improved |
| Evans 1998[24–40] "HELP" | Type and dose of antibiotic No antibiotic treatment | USA | Same as developed | Rule-based and simple probabilistic | No | 1992–2000 | Hospital, ICU, PICU,[b] surgery | Comparative interventional, before–after; non comparative prospective, assessed against physician opinion and *in vitro* susceptibilities | Intermediary, non-patient-related end outcome and patient-related end outcomes | 1. Appropriate antibiotic treatment<br>2. Allergy and dosing alerts<br>3. Total antibiotic used<br>4. Antibiotic prophylaxis<br>5. Costs<br>6. Adverse events due to antibiotics | 1. Significantly Improved<br>2. Significantly reduced<br>3. No difference<br>4. Significantly improved<br>5. No difference<br>6. Significantly reduced |

(*Continued*)

TABLE 4.1. (*Continued*)

| Reference | Type of recommendation | Location developed | Location tested | Logical core | Eco[a] values | Year(s) tested | Setting | Trial design | Types of outcomes assessed | Specific outcomes | Systems' effects |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 7. Renal toxicity<br>8. Postsurgical infections<br>9. Mortality | 7. Significantly reduced<br>8. Significantly reduced<br>9. No difference |
| Gierl 2003[41, 42] "ICONS" | Type and dose of antibiotic | Germany | No clinical testing | Case-based reasoning | No | No clinical testing | No clinical testing | Non comparative non interventional. Assessment against physician opinion | Intermediary | 1. Types of antibiotic used | 1. Inconclusive |
| Mullett 2004[43] | Type of antibiotic | USA | Same as developed | Case-based reasoning | Yes | 2002 | Hospital | Non comparative non interventional, retrospective. Assessment against *in vitro* susceptibilities | Intermediary | 1. Appropriate antibiotic treatment<br>2. Ecological impact<br>3. Number of different regimens | 1. Significantly improved<br>2. No difference<br>3. Significantly reduced |
| Samore 2005[44–46] | Type of antibiotic Dosing recommendation for pediatric patients | USA | Same as developed | Rule-based[c] | No[c] | 2002–2003 | Rural communities | Cluster-randomized trial; communities randomized; | Intermediary | 1. Total antibiotic use<br>2. Specific antibiotic class use | 1. Significantly reduced<br>2. Reduction in macrolide use |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | intervention on primary care clinicians | | 3. Unnecessary antibiotic treatment | 3. Significantly reduced |
| Thursky 2006[47, 48] | Type of antibiotic | Australia | Same as developed | Rule-based | No | 2002 | ICU | Comparative interventional, before–after | Intermediary and non-patient-related end outcomes | 1. Broad-spectrum antibiotic use | 1. Significantly reduced |
| | | | | | | | | | | 2. Appropriate antibiotic treatment[d] | 2. No difference overall |
| | | | | | | | | | | 3. Time to appropriate antibiotic treatment | 3. No difference |
| | | | | | | | | | | 4. Superfluous appropriate antibiotic treatment | 4. Significantly reduced |
| | | | | | | | | | | 5. Costs | 5. Reduced |

[a] Eco values—were ecological considerations explicitly taken into account when selecting the antibiotic/s regimen (e.g. impact of antibiotic selection on future resistance)?

[b] ICU, intensive care unit; PICU, pediatric intensive care unit.

[c] Decision support was provided electronically (hand-held personal digital assistant) to 78% of physicians in the intervention arm, the remaining using paper-based decision support. Ecological considerations taken into account inexplicitly in the guideline-based rules recommended by the system.

[d] Given an identified isolate and assessing all isolates, whether clinically significant or not.

TABLE 4.2. Antibiotic computerized decision support systems providing advice on antibiotic dosing/administration

| Reference | Location | Drug(s) | Trial design | Types of outcomes | Specific outcomes | Systems' effects |
|---|---|---|---|---|---|---|
| Sarubbi 1978[49] | USA | Aminoglycoside dosing | Noncomparative prospective, interventional Comparison to drug levels | Intermediary | 1. Drug levels | 1. Safe. System's predicted drug level matched measured drug levels |
| de Repentigny 1981[50] | Canada | Aminoglycoside dosing | Noncomparative prospective, interventional Comparison to drug levels | Intermediary | 1. Drug levels | 1. Adequate |
| Begg 1989[51, 52] | New Zealand | Aminoglycoside dosing | Two randomized controlled trials | Intermediary | 1. Drug levels | 1. Significantly improved |
| Burton 1991[53] | USA | Aminoglycoside dosing | Crossover, randomized controlled trial; physicians randomized | Intermediary, non-patient-related end outcome and patient-related end outcome | 1. Drug levels<br>2. Costs<br>3. Renal toxicity<br>4. Response to treatment<br>5. Hospitalization duration<br>6. Infection-related mortality | 1. Better than control<br>2. Nonsignificantly reduced<br>3. Nonsignificantly reduced<br>4. Nonsignificantly improved<br>5. Significantly reduced<br>6. Nonsignificantly reduced |
| Lenert 1992[54, 55] ATM | USA | Aminoglycoside dosing | Noncomparative prospective, noninterventional Comparison to physician | Intermediary | 1. Agreement with expert | 1. Inconclusive |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hulgan 2004[56] WizOrder | USA | Quinolone administration (oral/intravenous) | Comparative interventional, before–after | Intermediary and non-patient-related end outcomes | 1. Oral quinolone use<br>2. Costs | 1. Significantly increased<br>2. Significantly reduced |
| MacGregor 2006[57] | USA | Alerts for all antibiotics | Randomized controlled trial Patients randomized | Intermediary, non-patient-related end outcomes and patient-related end outcomes | 1. Testing for *Clostridium difficile*<br>2. Costs<br>3. Consultation time<br>4. In-hospital mortality<br>5. Length of stay | 1. No difference<br>2. Reduced<br>3. Reduced<br>4. No difference<br>5. No difference |

could assess only intermediary outcomes and showed a significant improvement in appropriate antibiotic treatment compared to the treatment actually administered to the patient by physicians. Two systems were tested in comparative before–after studies.[24–40, 47, 48] The system (HELP) was developed at LDS hospital and includes several decision support modules, including antibiotic selection in the ICU, antibiotic dosing, allergy mismatch alerting, and surgical antibiotic prophylaxis. The system was tested in several noninterventional trials.[24–40] Two versions of the antibiotic selection module were tested in before–after trials in an adult and a pediatric ICU.[24, 29] Overall, the assessment of the different modules in the HELP system showed significant improvements in appropriate antibiotic treatment and significant reductions in excessive antibiotic dosing, allergy mismatches, postoperative infections, adverse events, and renal toxicity. Thursky et al. assessed a decision support system designed to assist ICU clinicians at the time microbiological results are available, in a before–after study.[47, 48] The main outcomes were intermediary and the study showed a reduction in broad-spectrum and superfluous antibiotics while maintaining the rate appropriate antibiotic treatment. A single system was tested in a randomized controlled trial.[44–46] The trial was cluster randomized and assigned rural communities to community-based educational intervention versus stand-alone decision support tools on paper or a hand-held personal digital assistant. Only intermediary outcomes were assessed in this trial that showed a reduction in total, and nonindicated antibiotic use.

Two systems did not reach clinical testing. MYCIN, developed between 1975 and 1979, was a rule-based system designed to assist the diagnosis and selection of antibiotics for meningitis and bacteremia. The meningitis module was assessed in 10 selected cases against physicians, experts, and *in vitro* results.[20] ICONS, more recently developed (1993–1996), was designed to provide comprehensive support for the selection and dosing of antibiotics through case-based reasoning.[41, 42] However, the system's evaluation was poor. The system's advice was compared with physician's antibiotic selection in 20 cases without bacteriological confirmation. As with all other comparisons against physician performance, results were inconclusive since no gold standard was available.

Twelve systems designed to assist antibiotic selection were developed but never tested. Lucas et al. designed a system to diagnose and treat pneumonia in mechanically ventilated patients based on a causal probabilistic network (PTA).[58] The diagnostic performance of the system was assessed, showing an adequate capability to diagnose ventilator-associated pneumonia.[59] Antibiotic selection was not tested, since the model balancing benefits and costs of the antibiotics was not completed.

None of the systems were clinically tested in a site different than the site in which they were developed. Patient-related end outcomes were reported in the single comparative trial (the HELP system).[29] We could not find in these reports information as to the implementation of these systems in clinical practice. Parts of the HELP system have been in routine clinical use at LDS hospital for three decades, although clinical use of the antibiotic selection module has not been described.

### Antibiotic Dosing Systems

Seven systems were designed to assist with dosing or method of administration of antibiotics (Table 4.2). Five systems recommended on aminoglycoside dosing,[49–55] one was designed to suggest oral administration of quinolones when possible,[56] and one system issued various antibiotic alerts including, for example, equivalent oral antibiotics, treatment-susceptibility mismatches, or double antibiotic coverage.[57] These systems were tested mostly in clinical trials, including four randomized controlled trials. However, only two trials examined patient-related end outcomes: one aminoglycoside dosing study showed a nonsignificant reduction in adverse events, nonsignificant improvement in response to treatment, and a significant reduction in length of hospital stay,[53] and the antibiotic alert system trial reported no significant difference in length of stay and in-hospital mortality.[57] All of the aminoglycoside trials showed improved therapeutic drug levels.

## The TREAT System

We developed and tested a decision support system (TREAT) for the antibiotic treatment of inpatients with community- and hospital-acquired infections.[60–65] The system is based on a causal probabilistic network. The network is modeled to diagnose the type and severity of infection based on individual clinical variables, such as measurements of temperature, blood pressure, and presence of cough. A causal probabilistic network includes variables and links. The links between the variables represent causality, in our case pathogenesis of infection. For example, the variable "lung infiltrate" is linked to the variable "*Streptococcus pneumoniae* in the lung." The direction of the link is causal, such that lung infiltrate is the result of "*Streptococcus pneumoniae* lung infection." The variables are represented as probabilities. These can be independent probabilities; the probability of "smoking," for example, is independent of other variables in the network. Most variables are dependent on other parent variables. Thus, the probability of "chronic lung disease" is dependent on "smoking" and the probability of "*Streptococcus pneumoniae* in the lung" is dependent on "chronic lung disease." The basic units of the model are pathogens.

In the TREAT system, we modeled 11 sites of infection (e.g., skin/soft tissues) and 34 different diagnoses (e.g., diabetic foot, cellulitis) representing common community-acquired and nosocomial infections. The system covers 155 pathogens and includes 214 other clinical variables and more than 8000 nodes. The probabilities for all variables are defined in the network based on extensive literature reviews and local data where appropriate.

Antibiotic treatment is selected based on a cost–benefit model. Single and combination antibiotic treatments are ranked by cost–benefit and the regimen with the highest benefit–cost difference is recommended for treatment. Benefit consists of the coverage of the antibiotic/s, given the likely spectrum of pathogens predicted by the network. Coverage is converted to gain in life years and bed-days based on actual data showing an independent reduction in mortality with appropriate

empirical antibiotic treatment (OR = 1.6) and a reduction is hospital stay (3 days).[6] The costs of antibiotic treatment are derived from a complex model including an estimation of the ecological cost of antibiotic therapy: Total antibiotic costs equal to the sum of direct antibiotic costs (pharmacy cost, administration, monitoring), costs related to expected antibiotic-related side effects, and ecological costs. Ecological costs were calculated using data showing the quantitative association between antibiotic use and resistance induction for specific antibiotics and accounting for local baseline prevalence of resistance to the specific antibiotic and its use.

An explicit part of the system is a calibration component. We planned a system that can be calibrated to different locations and time. We thus predefined those variables within the network and the cost–benefit model that will necessitate secular adjustment. These variables are placed in TREAT's calibration databases, allowing for a semiautomatic calibration of the complete system. Thus, when transferred from place to place, local bacterial susceptibility patterns are adjusted, the types of antibiotics used and their costs are calibrated, the prevalences of pathogens causing nosocomial infections are changed, and so on. These same mechanisms can be used for temporal calibration.

In clinical practice, data available at the time the patient is seen are entered in the system. Input data used by the system include demographic variables, background diseases and conditions, signs and symptom of sepsis and local infection, microbiological data, radiography, other specific diagnostic tests such as serology or direct antigen tests, and previous antibiotic treatment. The system uses as much data as available, relying on preexisting probabilities present in the network for missing data. Output includes the overall probability of infection and probabilities for specific diagnoses as predicted by the system. Single and combination antibiotic treatments are ranked by their benefit–cost difference, highlighting the top ranked antibiotic recommendation. The result screen provides the user with the possibility to view the projected coverage and all cost–benefit components for each antibiotic treatment.

The system can be used at several time points along the course of infection management. The main use of the system is at the empirical stage, before causative pathogens or their susceptibilities are known. At this stage, the system uses mainly clinical data and predicts all microbiological outcomes, although available microbiological results may be used (e.g., cerebrospinal fluid Gram stain results). After 24–48 hours, the microbiology laboratory may report preliminary blood culture results, including growth and morphology. These results are added to previously stored data in the TREAT system and the systems' prediction and advice are updated to these new results. Finally, all microbiological results become available, including pathogen identification and susceptibility testing results. At this stage, antibiotic treatment may seem trivial, dictated by microbiological results. However, the system may be useful also at this stage. It will distinguish between infection causing disease and infection representing colonization; it will select the antibiotic regimen with the optimal cost–benefit given known microbiology and local ecological considerations; and it will enter pharmacokinetic and pharmacodynamic considerations into the final antibiotic choice. Examples of the system's results are shown in Figure 4.1.

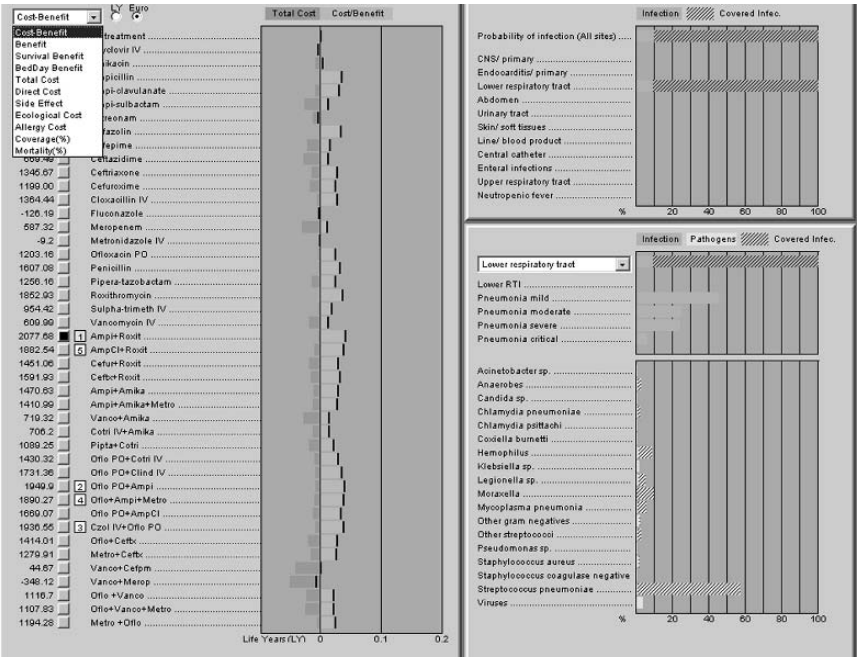
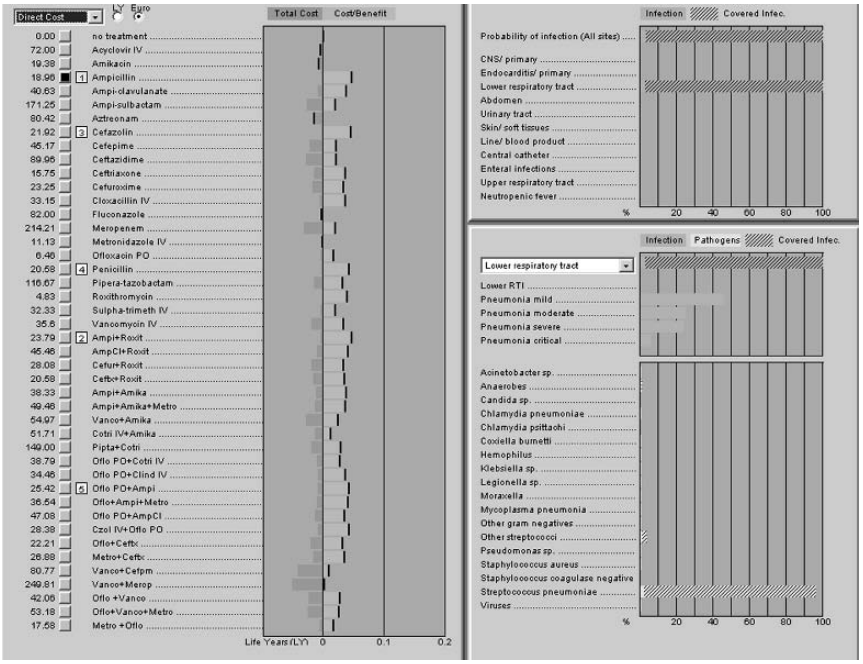



FIGURE 4.1. TREAT's result interface.

(A) A 65 year-old woman is admitted with fever up to 40 °C and chills. She is previously healthy. On admission, she is tachypneic with 20 breaths/minute, normotensive, oriented to place and time, with no signs of organ hypoperfusion. Her complaints include dyspnea, productive cough, and nonspecific chest pain. Laboratory findings on admission include a blood count showing 20,000 WBC/μl, albumin 3.4 g/dl, creatinine 1.2, and an erythrocyte sedimentation rate of 80 mm/hr. Other results are within normal limits. Urinalysis shows 500 WBC/μl, 250 RBC/μl, and positive nitrates. A chest x-ray shows an RLL lobar infiltrate. TREAT uses all the data provided above and generates the advice shown in the upper panel. The probability for infection is 100%, the source is lower respiratory tract, and the diagnosis is pneumonia. Pneumonia severity probabilities are shown below the diagnosis, with mild pneumonia corresponding to Fine class I and II, moderate, severe, and critical to Fine classes III, IV, and V, respectively. The predicted pathogen distribution for this patient is shown below the diagnosis, with *Streptococcus pneumoniae* most probable. To the left, single and combination antibiotic treatments are shown with the cost–benefit values for each treatment. The top five treatment options are enumerated. Ampicillin + roxithromycin is selected as the top choice for its highest benefit–cost difference. The system shown was calibrated for Israel. Users can select different viewing options from the upper left-hand drop-down box. With the selected view, the coverage provided by ampicillin + roxithromycin can be seen as the striped area over the infection and pathogen bars. Benefit minus cost difference values in Euros can be inspected to the left of each antibiotic treatment. Bars to the left of the null cost benefit line represent total costs for each treatment (summing direct, side effect, and ecological costs), bars to the right indicate total benefit (summing the gain in survival and hospital days), and the black bar represens overall cost–benefit. On screen, the result interface is colored simplifying interpretation of the bars and graph.




(B) forty-eight hours after admission new microbiological data become available. Gram-positive cocci in chains are reported in blood cultures and the urine sample grew *E. coli* $10^5$/HPF resistant to ampicillin and co-trimoxazole, susceptible to quinolones, nitrofurantoin, and second- and third-generation cephalosporins. These data are added to the TREAT system, which provides the recommendations shown in Panel B. Diagnosis has not changed, but the probability for pneumococcal pneumonia increased from 56% to 96%. Consequently, suggested treatment changed to ampicillin alone. TREAT diagnosed the urinary findings on admission and the subsequent growth of *E. coli* in the urine as asymptomatic bacteriuria (not shown in figure), given the lack of urinary complaints. It did not treat this infection. Ampicillin was chosen for pneumococcal pneumonia, based on predefined susceptibilities in the network (and shown as shaded areas over the pathogen bars). In Panel B, direct antibiotic costs (Israeli calibration) were chosen as the viewing option and can be seen in Euros to the left of the antibiotic treatment options.

The system was tested in several phases. Clinical testing began with a prospective noninterventional trial conducted in three hospitals in Italy, Germany, and Israel.[65] Data on 1203 patients with suspected bacterial infections were collected prospectively. The data were presented to the TREAT system and its top-rank antibiotic choice was compared to *in vitro* susceptibilities and physicians' treatment. Physicians prescribed appropriate treatment (i.e., matching *in vitro* results) to 57% of patients with an identified bacterial pathogen, compared to 70% for TREAT, $p = 0.0001$, a relative increase of 21%. The system used a narrower an..tibiotic formulary and at lower costs than physicians, mainly lowering costs assigned by the model to future resistance. The system performed well in the three testing sites.

We then proceeded to a cluster-randomized controlled trial in the three locations.[65] Participating wards in each hospital were randomized to control or intervention. In intervention wards, the system was installed and its use was offered to physicians. Physicians were requested to enter data available prior to prescription of empirical antibiotic treatment and inspect TREAT's result interface. The final choice of antibiotic treatment was theirs. In control wards, all patients fulfilling inclusion criteria were prospectively identified and the same data were collected. We compared all included patients in intervention wards to all patients in control wards. The trial included 2326 patients. Intervention wards using TREAT achieved a higher rate of appropriate empirical antibiotic treatment while reducing overall antibiotic costs. The rate of appropriate empirical antibiotic treatment (in patients with a known pathogen) improved from 64% (176/273) in control to 73% (216/297) in intervention wards by intention to treat and to 85% per protocol (114/134, $p = 0.001$ adjusting for location and clustering). The median length of stay in intervention wards was shortened by one day. A major achievement attained was a reduction in ecological antibiotic costs among all patients in intervention wards (-12%, $p = 0.002$).

These trials assessed the system's performance at the empirical stage. The system's performance at the semiempirical stage, when blood culture morphology results become available, was tested in a retrospective study and in a before–after interventional trial. The retrospective trial was conduced in Denmark. In 917 cases of bacteremic urinary tract infection the system prescribed appropriate narrow-spectrum antibiotic treatment to 88.5% of patients, compared to 60.8% actually given appropriate antibiotics ($p = 0.01$).[60] The before–after trial was conducted in Germany. The system was installed in the microbiology laboratory and provided advice for patients with positive blood cultures when only morphology results were available. Compared to the period before implementation of the system, appropriate antibiotic treatment improved nonsignificantly from 78.4% to 87.1%.[66]

Looking at the experience available before TREAT, we targeted several innovations with our system. The first was the inclusion of explicit ecological costs in the model. Given the increasing problem of antibiotic resistance, ecological considerations must become an integral and decisive part of any intervention for antibiotic prescription. Thus, a computerized decision support system must incorporate not only data regarding local resistance patterns to adequately prescribe antibiotics, but also data regarding the differential and local ecological impact of the antibiotic(s) advised. We have shown a reduction in ecological costs as defined in the model. Assuming that these costs indeed represent the local antibiotic ecological value, we believe we have improved the ecology of the departments using TREAT. A longer follow-up would be required to actually assess the impact of the system on the ecology of the environment.

The second target was to develop a system that can be transferred from place to place and can be calibrated in time. TREAT was calibrated to three countries. The three locations differed with respect to patient case-mix, infection epidemiology, baseline resistance patterns, and users of the system. TREAT performed well in each location.

Finally, we wanted to test the system with adequate methodology. We collected and reported data on patient-related end outcomes by intention to treat. For the reasons detailed previously, we chose a cluster-randomized design. We were careful to adjust all comparisons to clustering in the statistical analysis of the trial.

We have identified places for further improvement. TREAT was underused in intervention departments. The system was activated only in about 60% of patients fulfilling inclusion criteria. Integrating the system into an electronic patient file and linking the system to the hospital's databases would improve physicians' compliance. The system suggested whether antibiotic treatment should be initiated and the type of antibiotic(s). Further development should include dosing suggestions with adjustments to creatinine clearance and other factors.

## Lessons Learned and the Future

The review of the literature with the addition of the newly developed TREAT system permits an overview of the state of the art with regard to computerized antibiotic decision support.

Only a handful of systems designed to assist antibiotic selection have reached any testing phase. Of these, only six reached clinical assessment. TREAT was the first and only system tested in a randomized trial in multiple locations. None of the systems are in routine clinical use. Twice as many systems have been developed, but not tested. Our analysis is limited by information found in published literature and our own data. We limited our analysis to systems that have been tested. It is not possible to assess a system, even if fully developed and described, without some demonstration of its performance. Reaching the testing phase provides some proof that the system's development is complete, not a simple task in antibiotic computerized decision support.

All systems showed improvement over physicians' performance with regard to prescription of appropriate antibiotic treatment. The systems achieved appropriate treatment by improving diagnosis, better prediction of causative pathogens or better matching to local antibiotic susceptibilities. Appropriate empirical antibiotic treatment independently reduces all cause mortality and thus is a major achievement per se.[1–10]

However, appropriate antibiotic advice alone is insufficient. Some balance between the gain of covering treatment and antibiotic costs must be achieved. The major cost to consider is the impact of the antibiotic choice on future antibiotic resistance. However, this component is largely missing in existing systems. No model currently exists to quantify the ecological impact of antibiotic treatment. Such a model should include the differential effect of the different antibiotics on the individual, on the environment, on resistance to the same antibiotic, and on resistance to other classes of antibiotics. It should be sensitive to temporal and local changes in resistance, since the ability of an antibiotic to induce resistance probably reaches a plateau at some resistance level. Only three decision support systems included an explicit representation of "ecological costs" in this balance. Two systems broadly

ranked antibiotics by ecological value, while in TREAT we attempted to model a quantitative value for ecological costs. Thus, experience with ecological modeling is minimal. For computerized antibiotic decision support a robust model is needed.

Systems designed to assist with drug dosing and the HELP system, providing more comprehensive prescription support, show that computerized systems can prevent prescription errors. These systems performed better than physicians and improved patient-related outcomes. These systems have been adequately tested and their use should be encouraged.

Existing and future decision support systems should strive to accomplish comprehensive support for antibiotic prescription. The aspects demonstrated individually in previous systems should be combined. Support with regard to type of antibiotic treatment should be combined with dosing assistance. To enter clinical use, these systems should be integrated into an electronic patient file.

Adequate methodology for testing, analysis, and reporting of trials to assess the performance of decision support systems must be developed. The special features of these complex interventions impose methods that differ from those used to assess drugs. Specifically, the design of future trials should take into account the educative aspect of the system, assessment of patient-related outcomes, and assessment of the system's impact on resistance.

Comprehensive computerized antibiotic decision support should be used to fight antibiotic resistance. Limiting unnecessary antibiotic use, better dosing, improving directed and appropriate antibiotic treatment can optimize antibiotic therapy. We hope that these systems will help improve antibiotic stewardship and fight antibiotic resistance development.

## *References*

1. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* 2003; 31: 2742–51.
2. Hanon FX, Monnet DL, Sorensen TL, Molbak K, Pedersen G, Schonheyder H. Survival of patients with bacteraemia in relation to initial empirical antimicrobial treatment. *Scand J Infect Dis* 2002; 34: 520–8.
3. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003; 115: 529–35.
4. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118: 146–55.
5. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: Risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother* 2005; 49: 760–6.
6. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; 244: 379–86.

7. Pazos Anon R, Fernandez Rodriguez R, Tinajas A, Nanin C, Bustillo M, Paz I, Barreiro R, Gayoso Diz P. [Antimicrobial susceptibility of the bloodstream infections: A study in a nonteaching hospital]. *An Med Intern* 2004; 21: 483–7.
8. Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: Impact of shock and inappropriate antibiotic therapy on survival. *Chest* 2003; 123: 1615–24.
9. Zaidi M, Sifuentes-Osornio J, Rolon AL, Vazquez G, Rosado R, Sanchez M, Calva JJ, de Leon-Rosales SP. Inadequate therapy and antibiotic resistance. Risk factors for mortality in the intensive care unit. *Arch Med Res* 2002; 33: 290–4.
10. Pedersen G, Schonheyder HC, Sorensen HT. Source of infection and other factors associated with case fatality in community-acquired bacteremia—A Danish population-based cohort study from 1992 to 1997. *Clin Microbiol Infect* 2003; 9: 793–802.
11. Leibovici L, Wysenbeek AJ. Single-dose antibiotic treatment for symptomatic urinary tract infections in women: A meta-analysis of randomized trials. *Q J Med* 1991; 78: 43–57.
12. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; 40: 643–54.
13. Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev* 2003; CD003038.
14. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: A systematic review. *Arch Intern Med* 2003; 163: 1409–16.
15. Koppel R, Metlay JP, Cohen A, Abaluck B, Localio AR, Kimmel SE, Strom BL. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005; 293: 1197–203.
16. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: A systematic review. *JAMA* 1998; 280: 1339–46.
17. Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: A systematic review. *JAMA* 2005; 293: 1223–38.
18. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: A systematic review of trials to identify features critical to success. *Br Med J* 2005; 330: 765.
19. Ramsay C, Brown E, Hartman G, Davey P. Room for improvement: A systematic review of the quality of evaluations of interventions to improve hospital antibiotic prescribing. *J Antimicrob Chemother* 2003; 52: 764–71.
20. Yu VL, Fagan LM, Wraith SM, Clancey WJ, Scott AC, Hannigan J, Blum RL, Buchanan BG, Cohen SN. Antimicrobial selection by a computer. A blinded evaluation by infectious diseases experts. *JAMA* 1979; 242: 1279–82.
21. Wraith SM, Aikins JS, Buchanan BG, Clancey WJ, Davis R, Fagan LM, Hannigan JF, Scott AC, Shortliffe EH, van Melle WJ, Yu VL, Axline SG, Cohen SN. Computerized consultation system for selection of antimicrobial therapy. *Am J Hosp Pharm* 1976; 33: 1304–8.
22. Yu VL, Buchanan BG, Shortliffe EH, Wraith SM, Davis R, Scott AC, Cohen SN. Evaluating the performance of a computer-based consultant. *Comput Programs Biomed* 1979; 9: 95–102.

23. Leibovici L, Gitelman V, Yehezkelli Y, Poznanski O, Milo G, Paul M, Ein-Dor P. Improving empirical antibiotic treatment: Prospective, nonintervention testing of a decision support system. *J Intern Med* 1997; 242: 395–400.
24. Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and impact of a computerized pediatric antiinfective decision support program. *Pediatrics* 2001; 108: E75.
25. Antibiotic-related ADEs plummet and pharmacy costs shrink with computer-aided decision support. *Clin Resour Manag* 2000; 1: 151–3.
26. Burke JP, Pestotnik SL. Antibiotic use and microbial resistance in intensive care units: Impact of computer-assisted decision support. *J Chemother* 1999; 11: 530–5.
27. Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Ann Pharmacother* 1999; 33: 1026–31.
28. Warner H Jr, Reimer L, Suvinier D, Li L, Nelson M. Modeling empiric antibiotic therapy evaluation of QID. *Proc AMIA Symp* 1999; 440–4.
29. Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF Jr, Lloyd JF, Burke JP. A computer-assisted management program for antibiotics and other antiinfective agents. *N Engl J Med* 1998; 338: 232–8.
30. Warner H Jr, Blue SR, Sorenson D, Reimer L, Li L, Nelson M, Barton M, Warner H. New computer-based tools for empiric antibiotic decision support. *Proc AMIA Annu Fall Symp* 1997; 238–42.
31. Pestotnik SL, Classen DC, Evans RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: Clinical and financial outcomes. *Ann Intern Med* 1996; 124: 884–90.
32. Evans RS, Classen DC, Pestotnik SL, Clemmer TP, Weaver LK, Burke JP. A decision support tool for antibiotic therapy. *Proc Annu Symp Comput Appl Med Care* 1995; 651–5.
33. Evans RS, Classen DC, Pestotnik SL, Lundsgaarde HP, Burke JP. Improving empiric antibiotic selection using computer decision support. *Arch Intern Med* 1994; 154: 878–84.
34. Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother* 1994; 28: 523–7.
35. Evans RS, Pestotnik SL. Applications of medical informatics in antibiotic therapy. *Adv Exp Med Biol* 1994; 349: 87–96.
36. Evans RS, Pestotnik SL, Classen DC, Burke JP. Development of an automated antibiotic consultant. *MD Comput* 1993; 10: 17–22.
37. Evans RS. The HELP system: A review of clinical applications in infectious diseases and antibiotic use. *MD Comput* 1991; 8: 282–8, 315.
38. Burke JP, Classen DC, Pestotnik SL, Evans RS, Stevens LE. The HELP system and its application to infection control. *J Hosp Infect* 1991; 18 Suppl A: 424–31.
39. Evans RS, Pestotnik SL, Burke JP, Gardner RM, Larsen RA, Classen DC. Reducing the duration of prophylactic antibiotic use through computer monitoring of surgical patients. *DICP* 1990; 24: 351–4.
40. Larsen RA, Evans RS, Burke JP, Pestotnik SL, Gardner RM, Classen DC. Improved perioperative antibiotic use and reduced surgical wound infections through use of computer decision analysis. *Infect Control Hosp Epidemiol* 1989; 10: 316–20.
41. Gierl L, Steffen D, Ihracky D, Schmidt R. Methods, architecture, evaluation and usability of a case-based antibiotics advisor. *Comput Methods Programs Biomed* 2003; 72: 139–54.
42. Schmidt R, Gierl L. Case-based reasoning for antibiotics therapy advice: An investigation of retrieval algorithms and prototypes. *Artif Intell Med* 2001; 23: 171–86.

43. Mullett CJ, Thomas JG, Smith CL, Sarwari AR, Khakoo RA. Computerized antimicrobial decision support: An offline evaluation of a database-driven empiric antimicrobial guidance program in hospitalized patients with a bloodstream infection. *Int J Med Inform* 2004; 73: 455–60.
44. Samore MH, Bateman K, Alder SC, Hannah E, Donnelly S, Stoddard GJ, Haddadin B, Rubin MA, Williamson J, Stults B, Rupper R, Stevenson K. Clinical decision support and appropriateness of antimicrobial prescribing: A randomized trial. *JAMA* 2005; 294: 2305–14.
45. Madaras-Kelly KJ, Hannah EL, Bateman K, Samore MH. Experience with a clinical decision support system in community pharmacies to recommend narrow-spectrum antimicrobials, nonantimicrobial prescriptions, and OTC products to decrease broad-spectrum antimicrobial use. *J Manag Care Pharm* 2006; 12: 390–7.
46. Rubin MA, Bateman K, Donnelly S, Stoddard GJ, Stevenson K, Gardner RM, Samore MH. Use of a personal digital assistant for managing antibiotic prescribing for outpatient respiratory tract infections in rural communities. *J Am Med Inform Assoc* 2006; 13: 627–34.
47. Thursky KA, Buising KL, Bak N, Macgregor L, Street AC, Macintyre CR, Presneill JJ, Cade JF, Brown GV. Reduction of broad-spectrum antibiotic use with computerized decision support in an intensive care unit. *Int J Qual Health Care* 2006; 18: 224–31.
48. Thursky KA, Mahemoff M. User-centered design techniques for a computerised antibiotic decision support system in an intensive care unit. *Int J Med Inform* 2006;
49. Sarubbi FA Jr, Hull JH. Amikacin serum concentrations: Prediction of levels and dosage guidelines. *Ann Intern Med* 1978; 89: 612–8.
50. de Repentigny L, Dumont L, Le Lorier J, Morisset R, Larochelle P, Courchesne Y. Gentamicin: Use of a programmable calculator to determine dosages from pharmacokinetic data for individual patients. *Can Med Assoc J* 1981; 124: 1459–63.
51. Begg EJ, Atkinson HC, Jeffery GM, Taylor NW. Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations. *Br J Clin Pharmacol* 1989; 28: 137–41.
52. Hickling K, Begg E, Moore ML. A prospective randomised trial comparing individualised pharmacokinetic dosage prediction for aminoglycosides with prediction based on estimated creatinine clearance in critically ill patients. *Intensive Care Med* 1989; 15: 233–7.
53. Burton ME, Ash CL, Hill DP Jr, Handy T, Shepherd MD, Vasko MR. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. *Clin Pharmacol Ther* 1991; 49: 685–94.
54. Lenert LA, Klostermann H, Coleman RW, Lurie J, Blaschke TF. Practical computer-assisted dosing for aminoglycoside antibiotics. *Antimicrob Agents Chemother* 1992; 36: 1230–5.
55. Lenert LA, Lurie J, Sheiner LB, Coleman R, Klostermann H, Blaschke TF. Advanced computer programs for drug dosing that combine pharmacokinetic and symbolic modeling of patients. *Comput Biomed Res* 1992; 25: 29–42.
56. Hulgan T, Rosenbloom ST, Hargrove F, Talbert DA, Arbogast PG, Bansal P, Miller RA, Kernodle DS. Oral quinolones in hospitalized patients: An evaluation of a computerized decision support intervention. *J Intern Med* 2004; 256: 349–57.
57. McGregor JC, Weekes E, Forrest GN, Standiford HC, Perencevich EN, Furuno JP, Harris AD. Impact of a computerized clinical decision support system on reducing inappropriate antimicrobial use: A randomized controlled trial. *J Am Med Inform Assoc* 2006; 13: 378–84.

58. Lucas PJ, de Bruijn NC, Schurink K, Hoepelman A. A probabilistic and decision-theoretic approach to the management of infectious disease at the ICU. *Artif Intell Med* 2000; 19: 251–79.
59. Schurink CA, Lucas PJ, Hoepelman IM, Bonten MJ. Computer-assisted decision support for the diagnosis and treatment of infectious diseases in intensive care units. *Lancet Infect Dis* 2005; 5: 305–12.
60. Kristensen B, Andreassen S, Leibovici L, Riekehr C, Kjaer AG, Schonheyder HC. Empirical treatment of bacteraemic urinary tract infection. Evaluation of a decision support system. *Dan Med Bull* 1999; 46: 349–53.
61. Andreassen S, Leibovici L, Paul M, Nielsen A, Zalounina A, Kristensen L, Falborg K, Kristensen B, Frank U, Schonheyder H. A probabilistic network for fusion of data and knowledge in clinical microbiology, in Husmeier D, Dybowski R, Roberts S (eds): *Probabilistic Modeling in Bioinformatics and Medical Informatics*. London, Springer-Verlag, 2004, pp 451–72.
62. Andreassen S, Riekehr C, Kristensen B, Schonheyder HC, Leibovici L. Using probabilistic and decision-theoretic methods in treatment and prognosis modeling. *Artif Intell Med* 1999; 15: 121–34.
63. Leibovici L, Fishman M, Schonheyder HC, Riekehr C, Kristensen B, Shraga I, Andreassen S. A causal probabilistic network for optimal treatment of bacterial infections. *IEEE Trans Knowledge Data Eng* 2000; 12: 517–28.
64. Paul M, Andreassen S, Nielsen AD, Tacconelli E, Almanasreh N, Fraser A, Yahav D, Ram R, Leibovici L. Prediction of bacteremia using TREAT, a computerized decision-support system. *Clin Infect Dis* 2006; 42: 1274–82.
65. Paul M, Andreassen S, Tacconelli E, Nielsen AD, Almanasreh N, Frank U, Cauda R, Leibovici L. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: Cluster randomized trial. *J Antimicrob Chemother* 2006;58: 1238–45
66. Frank U, Almanasreh N, Nielsen A, Andreassen S, Tacconelli E, Cauda R, Paul M, Leibovici L. TREAT: An electronic consultant for the clinical microbiologist, in *44th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2004*, American Society for Microbiology.

*This page intentionally blank*

# Chapter 5
# Prevalence Surveys of Antimicrobial Use in Hospitals: Purpose, Practicalities, and Pitfalls

R. Andrew Seaton

## Introduction

Antimicrobials are widely used in hospitals for a broad range of conditions by a variety of specialists. Prescribing is largely empiric and is dependent on the recognition of clinical syndromes and the prescribers' experience, including their own awareness of likely causative microbes, local resistance profiles and their knowledge of antimicrobial therapy. As the majority of prescribers work in system-based specialities, their interest and expertise in microbiology and antimicrobial therapy is variable.[1] These factors may at least partly explain the observed variation and quality in prescribing practice.[2, 3]

Various interventions can be performed to support prescribing decisions and protect against antimicrobial overuse. These include restrictions on prescribing through formularies, guidelines, protocols, antibiotic restriction programs, and computerized treatment algorithms.[4–7] Such interventions can limit inappropriate (usually empiric) prescribing and can also play an important role in prescriber education. In addition, infection specialists in microbiology, infectious diseases, and pharmacy can input more directly into the antimicrobial management of patients, particularly where a microbe has been isolated, antibiotic therapy is failing, or complex infection is recognized.[8–11]

## Why Measure Antibiotic Use in Hospitals?

In an increasingly demanding modern healthcare system, prescribers and healthcare institutions have a responsibility to ensure that the valuable resource of antimicrobials is used prudently and effectively. An assessment of the appropriateness of prescribing is impossible without monitoring which antimicrobials are used and for whom. Surveys of prescribing should be an integrated part of any hospitals antimicrobial utilization strategy and ideally should be set in a regional or national framework.[12] Information gathered should inform and direct policy and dovetail with broader infection control issues.

Prescribing can broadly be measured by quantity (of an agent prescribed) and by quality (appropriateness of an agent for a given indication). The quantity (or volume) of a specific agent prescribed or dispensed is most usefully measured by calculating the defined daily dose (DDDs) per 1000 patient bed days.[13] This gives a picture of the pressure of a particular agent on a defined population and takes into account clinical activity for a specific period. This method, however, does not reflect the *quality* of prescribing in an individual patient or indeed population of patients. It is the measurement of the quality of prescribing which will be the focus for this chapter.

## Why Measure the Quality of Prescribing?

For an individual patient there are clear advantages to quality in prescribing of antibiotics. These include: assurance that the most effective therapy is being given, the chance that outcome (death/disability) is improved,[14–16] reduction in the risk of an antimicrobial–related adverse event and minimization of unnecessary treatment (e.g., reduction in duration of intravenous therapy). For the healthcare system, higher quality prescribing ensures better streamlining of prescribing (particularly inappropriate empirical intravenous use and timely intravenous-to-oral switch)[5–11] and should ensure reduction in risk of poor outcome or adverse event. Quality of prescribing can also include aspects of corporate responsibility such as prudence in prescribing of specific agents which may be prohibitively expensive or which may exert a disproportionate pressure on hospital microbes.

## The Prescribing Pathway

Prescribing in hospitals is a dynamic and complex process (Figure 5.1). Multiple factors influence the choice and the route of administration of an agent. These steps include:

1. The experience and knowledge of the prescriber
   a. The recognition of the condition and its severity
   b. Knowledge of the probability of a particular organism (and its resistance profile) causing a given condition
   c. Knowledge about utility of antibiotics in different situations (clinical pharmacology)
2. Local measures to influence antimicrobial prescribing
   a. Availability of antimicrobials (formulary)
   b. Availability of antimicrobials and sepsis management guidelines and protocols
   c. Implementation of guidelines and protocols
   d. Availability of expert antimicrobial advice (pharmacy, microbiology, and infectious diseases)

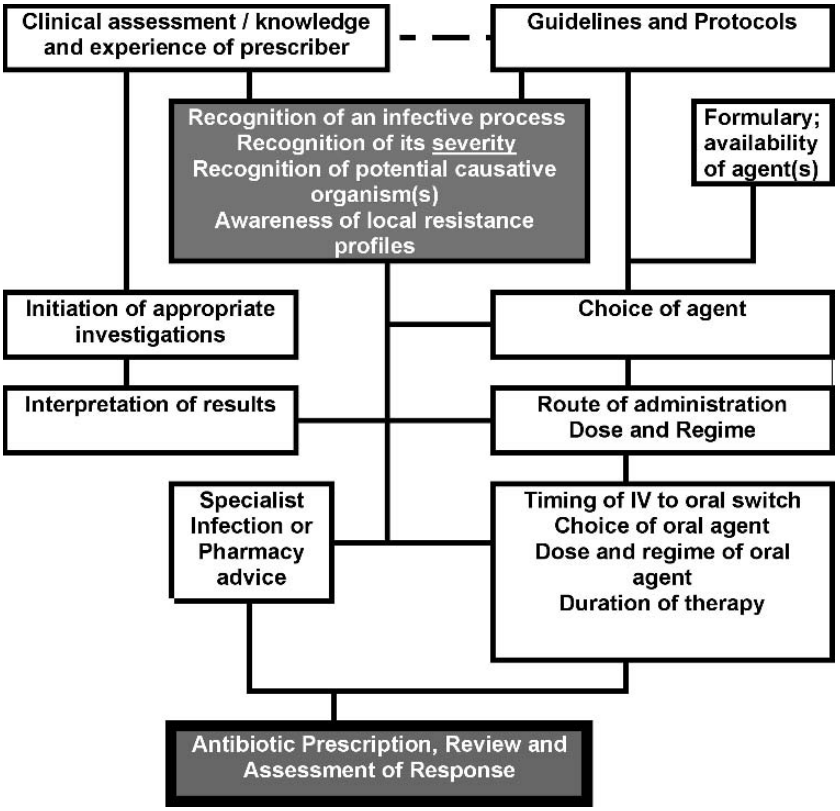



FIGURE 5.1. The antimicrobial prescribing pathway.

e. Specific local measures; restricted agents within formulary (e.g., alert agents requiring prior authorization), concurrent pharmacy initiated feedback on prescribing, automatic IV-to-oral switch protocols, etc.

3. National measures
   a. Public campaigns to limit prescribing
   b. Policy documents to control prescribing

Within the prescribing pathway it is clear that there are many potential steps that are amenable to audit. Some of these pertain to prescribing decisions by an individual, and some toward the system and prescribing policy.

The appropriateness of an antibiotic prescription could therefore be assessed in many different ways: Does the prescriber record the site/nature of the infection[17]? Are the appropriate investigations documented and process of care followed[18]? Is there evidence of understanding of basic pharmacology and microbiology (e.g., Is therapeutic drug monitoring done correctly)[2, 19]? Are the correct dose and dosing interval prescribed[2, 3]? Are agents with appropriate distribution, bioavailability and microbiological spectrum of activity used for the stated indication[20]? Is an intravenous agent selected when an oral agent would be appropriate[5]? Does

IV-to-oral switch occur early or late[5, 21–23]? Is an appropriate oral agent chosen following IV therapy[5]? Is the duration of therapy appropriate for the nature of the infection[24]? Does the prescriber follow local guidelines or protocols (when available)[2, 5, 18, 19, 25]? Does the prescriber adhere to advice when given by specialists in infection management[8–11, 24, 26, 27]?

The robustness of the local (hospital) antimicrobial management policy could likewise be assessed on different levels: Does the hospital adhere to regional or national guidelines for antimicrobial management policy[12]? Is there an antibiotic formulary and antibiotic or sepsis policy in place[4, 28]? Are there processes in place to support guideline adherence? Is expert antimicrobial advice available to prescribers from pharmacy, microbiology or infectious diseases? Are there other specific local measures in place to support prescribing such as

1. Alert agents (and supporting process) requiring prior authorization[6, 27]?
2. Concurrent pharmacy initiated feedback on prescribing[29]?
3. Nurse- or pharmacist initiated IV to oral switch protocols[30, 31]?
4. Specific information technology (IT) support for prescribing[7]?

## What Data Should Be Collected during an Antibiotic Prevalence Survey?

The simplest prevalence surveys record only the antibiotics prescribed by directly reviewing prescription charts. When electronic prescribing is in place, this process can potentially be more time-efficient.[32] Data generated give an indication of the range and volume of agents used as well as the duration of therapy and timing of IV-to-oral switch. Appropriate dosing and dosing interval can also be assessed. The major advantage of this type of survey is that the data are readily available and only one source needs to be searched. It also gives more detail than crude quantitative methods of data recording but gives limited information on the quality of prescribing, as there is no linkage with clinical data. Unfortunately, multiple sources of data need to be searched to gather more detailed clinical information to correlate with the prescribing data. Usual sources, which should be readily available, are case notes and nursing observation charts but searching these sources may be time consuming.

To assess appropriateness of prescribing, data on the nature and severity of the infection should be collected.[33, 34] This includes details of antibiotic therapy received (start date, route of administration, and date of switch from IV to oral when appropriate) and the indication (as recorded in the case sheets) for antibiotic therapy. For convenience of analysis, patients can be classified as receiving antibiotics for prophylaxis (e.g., prior to orthopedic implant surgery) or for treatment of a site-specific infection. Classification of the site of infection will depend on data recorded by clinicians in case sheets and can be as specific or nonspecific as is required, e.g., respiratory tract infection (RTI), including pneumonia, exacerbation of chronic obstructive pulmonary disease, tuberculosis and upper respiratory tract

infection; urinary tract infection (UTI), including pyelonephritis, cystitis, epididymitis, etc; skin and soft tissue infection (SSTI), including wound infection, cellulitis, and bursitis; intra-abdominal infection (IAI), including intra-abdominal surgical sepsis, gastroenteritis, and biliary sepsis; deep-seated infection (DSI), including endocarditis, osteomyelitis, and central nervous system infection. Such data can usually be used to determine if the appropriate agent has been chosen for the site of infection. It is important to differentiate between patients where no diagnosis has been recorded ("Not documented") and where it is recorded that the source of infection is not known ("Not known"). The latter may justify more empiric prescribing.

More specific clinical data relating to the infective episode can also be gathered to determine if the agent or the route of administration of the antibiotic is appropriate. A typical data collection form (The Glasgow Antimicrobial Audit Tool or GAAT)[35] is shown in Figure 5.2 Such detailed clinical data include signs of sepsis (temperature $\geq$38 °C, tachycardia $>$ 90 beats per minute, blood pressure $\leq$90 mm Hg systolic, respiratory rate $>$ 20 per minute and white cell count $<$ 4 or $>$ 12/mm recorded within 24 hours of the day of the survey, signs of severe sepsis (including oliguria, suspected respiratory distress, acidosis, hepatic failure, reduced conscious level), and signs of severe pneumonia (pneumonia plus one or more of the following: respiratory rate $>$ 30 per minute, confusion, urea $>$ 7mmol/liter, diastolic blood pressure $\leq$60 mm Hg, and age $>$ 65 years[33]). Other data which give additional information on the appropriateness of the IV route of administration include whether the oral route is compromised due to swallow, vomiting, or absorption problems, the presence of a multiresistant organism (e.g., MRSA) or absence of an oral formulation of a drug (e.g., gentamicin). Putting all the clinical data together it is then possible to construct a clinical algorithm to determine the appropriateness of the route of administration (Figure 5.3).

## Coordinating an Antibiotic Point Prevalence Survey

Given the potential complexity of data collection, particularly if done over several hospital sites, a detailed guideline document should be available for users on how to administer and complete the survey tool. Meetings between those who are coordinating and collecting data should be held to clarify how clinical data should be collected and recorded. Ideally the audit tool should be piloted to ensure its suitability for the given situation. Clinical pharmacists are ideally suited to both coordinate and collect data. If a specialist antimicrobial pharmacist is employed, it is frequently within their remit to coordinate such surveys. Infection specialists (microbiologists and infectious disease physicians) or other clinicians with an interest in prescribing should collaborate with pharmacy to help ensure the broadest possible support for the initiative.[36] Data are usually collected by specialty-based pharmacists, potentially supported by others who have an interest in antimicrobial prescribing, e.g., infectious disease physicians/trainees, microbiology medical staff, and infection control

**Glasgow Antimicrobial Audit Tool– Antimicrobial Data Form** *Survey 1*

**Section 1: Patient Details**

| | | | | | |
|---|---|---|---|---|---|
| **Hospital:** | | Was the patient previously discharged from any hospital in the last 28 days? | Yes 5 | No 5 | Unknown 5 |
| **Ward:** | | Was the patient admitted from a nursing or residential home? | Yes 5 | No 5 | Unknown 5 |
| **Age:** | | Is the patient a boarder? | Yes 5 | No 5 | |
| **Gender:** | Male 5 Female 5 | Antimicrobial allergies recorded on prescription chart | Yes 5 | No 5 | |
| **Date of hospital admission:** | ___/___/2003 | Has treatment with ***alert antimicrobials*** been discussed with a microbiologist? | Yes 5 | No 5 | Unknown 5 |

**Section 2 Antimicrobial Indication:** *Tick the appropriate broad and specific indication. If you are unsure of the specific indication, or if it is not listed below, write the diagnosis as it appears in the medical notes in the space below.*

| **Broad indication:** | | **Specific indication:** | | | | | |
|---|---|---|---|---|---|---|---|
| Respiratory | 5 | Pneumonia (including LRTI) | 5 | Aspiration pneumonia | 5 | Exac COPD | 5 |
| | | URTI | 5 | Cystic fibrosis /bronchiectasis | 5 | TB (including ExPTB) | 5 |
| Urinary Tract | 5 | Lower UTI | 5 | Pyelonephritis | 5 | | |
| Skin/soft tissue | 5 | Bursitis | 5 | Cellulitis | 5 | Surgical site infection | 5 |
| | | Trauma/burn | 5 | Abscess | 5 | Deep soft tissue | 5 |
| Deep seated infection | 5 | Bone/joint | 5 | Endocarditis | 5 | Meningitis | 5 |
| | | Encephalitis | 5 | | | | |
| Abdominal/ Pelvic | 5 | Hepatobiliary | 5 | *C Diff* | 5 | *H pylori* eradication | 5 |
| | | Gastroenteritis | 5 | Other | 5 | | |
| Sepsis /infection source unknown | 5 | Neutropenic fever | 5 | Infection cause unknown | 5 | Mixed infection | 5 |
| Other | 5 | Notes unavailable | 5 | Not documented | 5 | Other | 5 |

**Section 3: Current antimicrobial prescribing** – *only record what is prescribed on the prescription chart for today*

| Antimicrobial | Date started | Route |
|---|---|---|
| | ____/____/2003 | Oral 5 (1) IV 5 (2) Other 5 |
| | ____/____/2003 | Oral 5 (1) IV 5 (2) Other 5 |
| | ____/____/2003 | Oral 5 (1) IV 5 (2) Other 5 |

**Section 4: Initial IV therapy:** *only record initial IV antimicrobial(s) prescribed for the current infective episode*

| Previous IV antimicrobial | Date started | Previous IV antimicrobial | Date started |
|---|---|---|---|
| | ____/____/03 | | ____/____/03 |
| | ____/____/03 | | ____/____/03 |

**SECTIONS 5, 6 AND 7 SHOULD ONLY BE COMPLETED FOR PATIENTS WHO ARE PRESCRIBED AN IV ANTIBIOTIC TODAY**

**Section 5 Indication for current IV therapy:** *Tick the appropriate box based on the preceding 24 hours or last available*

| | | | |
|---|---|---|---|
| **Temperature:** ≥ 38° or ≤ 36° | Yes 5 No 5 Not Documented 5 | **Systolic BP:** ≤ 90mmHg | Yes 5 No 5 Not Documented 5 |
| **Heart rate:** ≥ 90bpm | Yes 5 No 5 Not Documented 5 | **Diastolic BP:** ≤ 60mmHg | Yes 5 No 5 Not Documented 5 |
| **Respiratory rate:** ≥ 20/min | Yes 5 No 5 Not Documented 5 | **Urea:** ≥ 7mmol/L | Yes 5 No 5 Not Documented 5 |
| **WBC Count:** ≤ 4 or ≥ 12 x$10^9$/L | Yes 5 No 5 Not Documented 5 | **$PO_2$:** ≤ 8kPa | Yes 5 No 5 Not Documented 5 |

**Section 6: Use of IV route:** *Complete the information based on the patients' condition in the preceding 24 hours*

| | | | |
|---|---|---|---|
| Oral route compromised: *eg ↓ swallow, ↓ absorption, vomiting, unconscious, nil by mouth* | Yes 5 No 5 Unknown 5 | Deteriorating clinical condition | Yes 5 No 5 Unknown 5 |
| Patient immunosuppressed? | Yes 5 No 5 Unknown 5 If yes, please tick the appropriate reason: Malignancy 5 HIV 5 Steroids 5 Other immunosuppressive 5 | | |

**Section 7: Documented clinical symptoms:** *Please indicate which of the following were recorded in the case notes either 24 hours prior to or 24 hours after IV antimicrobial(s) prescribed*

| Unknown | Clinical sign | Yes |
|---|---|---|
| 5 | Acute confusion (4) | 5 |
| 5 | New AF (5) | 5 |
| 5 | | |

Yes 5 No 5
Yes 5 No 5 Unknown 5

PatientID
5555

FIGURE 5.2. The Glasgow Antimicrobial Audit Tool.

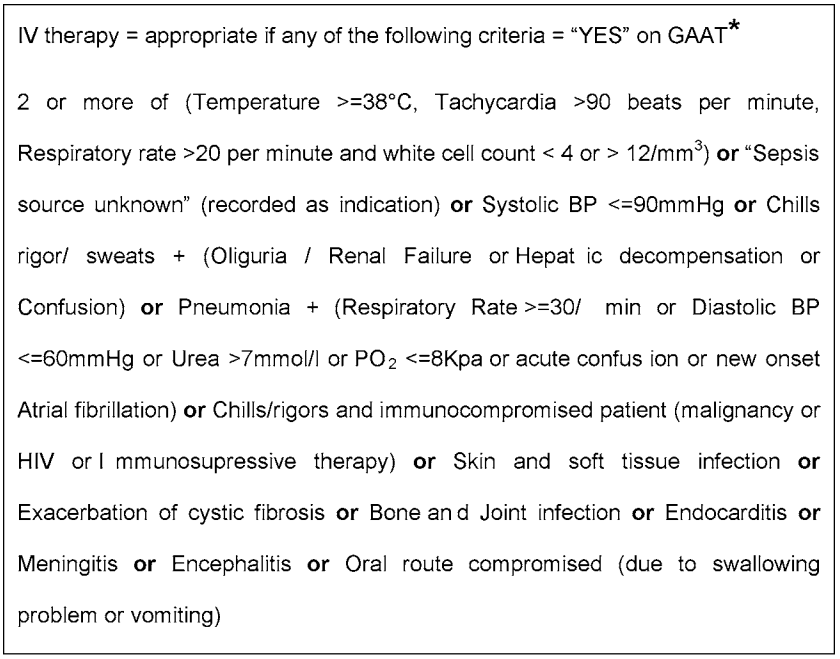



FIGURE 5.3. Clinical algorithm to determine appropriateness of IV therapy.

nurses, if manpower is limited. Generally when prevalence surveys are conducted, prescribers are not approached regarding individual prescriptions as this is prohibitively time consuming. Usually data are collected on a single site on a single day. It is important to plan which sites should be surveyed, and if long-term comparisons are anticipated, then data collection should be consistent. Care should be taken when making serial comparisons that the configuration of the specialist units has not changed between surveys and like is being compared with like. It is essential that once data have been collected the numbers of patients who have been screened for antimicrobial use be recorded, usually for each unit/ward surveyed. This allows for the calculation of the proportion of patients receiving antimicrobial therapy.

Ideally each hospital would have a dedicated program to collect and analyze and feed back data on prescribing and this would receive dedicated funding. In reality, most hospitals will perform antimicrobial audit within a generic budget using clinical pharmacy staff that perform multiple roles. It is therefore important to record the amount of time spent performing audit and to estimate the impact on the work load of a clinical pharmacy service.

## Data Analysis

Once collected, data should be scanned or inputted manually to a computerized database for analysis. Typically data detailing proportion of antibiotics prescribed, proportion of IV and oral therapy, duration of therapy, IV to oral switch timing and antibiotic indication and infection severity may be derived simply from the data set. Duration of IV therapy is calculated as the time from first prescription to the day of the survey. Subtle differences in duration of therapy may be calculated if the number of doses administered is recorded during the survey. Time from IV to oral switch can be calculated by selecting all those patients on oral therapy who had received prior IV therapy. An example of such a data set is shown in Table 5.1 which was adapted from a multisite survey in Scottish hospitals.[35]

It is also possible to develop algorithms within the database by generating a series of specific queries as shown in Figure 5.3. Such an algorithm may be used to generate an estimate of the appropriateness of IV therapy for each IV-treated patient. It may also be possible to "build in" criteria for certain agents to give an estimate of the appropriateness of the prescription of that particular agent. Although more cumbersome, it is also valid for infection specialists to review individual data collection forms and assess the appropriateness of a particular agent prescribed against local guidelines.

## Interpretation and Limitations of Data

Data derived from point prevalence surveys should be interpreted in context. By definition the data give a limited "snapshot" of clinical practice, which may not necessarily reflect everyday prescribing practice. The larger the number of

TABLE 5.1. Survey of Antibiotic Treatment in 10 Scottish hospitals[35].

| | | Total |
|---|---|---|
| All units | No. surveyed | 3826 |
| | No. receiving antibiotic treatment (%) | 1067 (28) |
| | No. of IV-treated patients (% of all AB treated) | 381 (35.3) |
| | Duration of IV therapy in days (median, IQR) | 4 (2–7) |
| | Time to oral switch in days (median, IQR) | 3.5 (2–6) |
| | Total number of IV antibiotics | 575 |
| Medicine | No. of antibiotic treated patients | 726 |
| | No. of IV-treated patients | 246 (33.9) |
| | Duration of IV therapy in days (median, IQR) | 4 (2–7) |
| | No. switched from IV to oral | 133 |
| | Time to oral switch in days (median, IQR) | 3 (2–5) |
| Surgery | No. of antibiotic treated patients | 326 |
| | No. of IV-treated patients | 123 (39) |
| | Duration of IV therapy in days (median, IQR) | 4 (2–6) |
| | No. switched from IV to oral | 64 |
| | Time to oral switch in days (median, IQR) | 4 (3–7) |

patients included, the greater is the validity of the survey. When a specific condition is targeted, e.g., community acquired pneumonia or infective exacerbations of chronic obstructive airways disease, the collection of more extensive clinical detail will ensure the usefulness of the survey [18]. The greatest value is derived when surveys can be repeated at regular intervals and trends in prescribing practice can be noted.[5, 6, 37, 38] Data derived can also indicate areas which may require more detailed investigation, e.g., certain units may be identified as using IV therapy for prolonged periods without obvious justification. Data may also indicate differences in antibiotic management of a common condition, e.g., community acquired pneumonia.[18, 39] Longer-term trends in the prescribing may be indicative of interventions to improve practice.[6, 7]

Multiple individuals derive data from multiple sources, so there is a potential danger of transcription error, which can be minimized by suitable training. Data, critical for a prescribing decision, may also be missing (unrecorded), e.g., phone call advice from an infection specialist or not included in the data set being collected, e.g., MRSA carriage in a patient with a soft tissue infection treated with vancomycin. Prescribing surveys could certainly be enhanced if microbiological data could be linked directly to the data set.

## Feedback of Data

It is critical that data is fed back both to prescribers and to those who are concerned with antimicrobial prescribing policy (Figure 5.4). When performing a point prevalence survey it is important to identify the most appropriate local pathway for

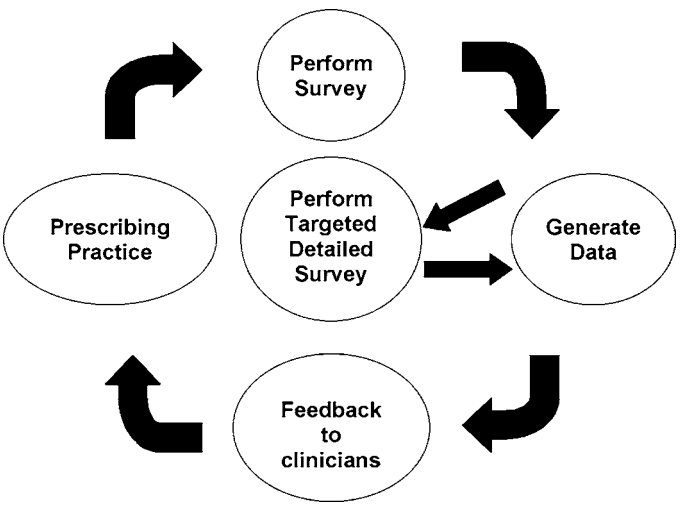



FIGURE 5.4. Feedback of survey data.

feeding back information about prescribing. Most healthcare systems are arranged around specialty groupings and within each of these groupings there should be a generic process for feedback of information. As well as feeding back through specialties there should be a process through clinical pharmacy for important data to be fed back to ward-based pharmacists and to prescribers. It is important that as well as feeding back concerns over prescribing, aspects of good prescribing practice should also be reported.

## Cost–Benefit Assessment of Antimicrobial Prevalence Surveys

In modern healthcare services new initiatives must compete for resources in an increasingly crowded marketplace. It is therefore important that when embarking on prevalence studies the costs and benefits are clearly identified and communicated to those who are responsible for funding and implementing change. Within this it is essential that there is the appropriate infrastructure to enable the data to be interpreted and communicated to prescribers and that the resources to implement change in prescribing are available.[12] The "costs" of prevalence surveys are outlined in Table 5.2 and can be summarized as additional personnel time and resources devoted to devising and performing the survey and inputting, analyzing, interpreting, and communicating the data. The benefits are to improve understanding of prescribing practice, identify areas of good and weak practice (to target further intervention and education), and monitor trends in prescribing of new and restricted agents. Also, the interaction and collaboration between pharmacists and infection specialists and other clinicians promotes an atmosphere of "prescribing awareness."

TABLE 5.2. Key steps in performing an antimicrobial point prevalence survey.

| |
|---|
| 1. Identify the patient group(s) or clinical syndrome(s) to be surveyed |
| 2. Agree objectives and time scale |
| 3. Agree clinical data set to be recorded |
| 4. Agree which sources of information should be accessed |
| 5. Agree how and to whom data should be communicated |
| 6. Identify team to collect data |
| 7. Identify a suitable date (seasonality) for survey |
| 8. Review survey method with team |
| 9. Consider pilot of survey (feasibility) |
| 10. Perform survey and record bed occupancy |
| 11. Input and clean data |
| 12. Analyze and interpret data |
| 13. Feed back data to clinicians and antimicrobial policy groups |
| 14. Review process |
| 15. Plan for follow-up (serial) survey |

## Conclusions

Measuring antimicrobial use and prescribing quality provides policymakers and prescribers alike essential information which can be used to inform, educate, and improve prescribing practice. Surveys of prescribing should be undertaken with clear aims and objectives and within an infrastructure that will support the proposed actions to be undertaken. The inclusion of, and collaboration between, clinical pharmacists, infection specialists, other clinicians, and policymakers in antimicrobial prescribing policy in general is key to developing and sustaining surveys of antimicrobial prescribing in hospitals.

## *References*

1. Srinivasan S, Song X, Richards A, Sinkowitz-Cochran R, Cardo D, Rand C. A survey of knowledge, attitudes, and beliefs of house staff physicians from various specialities concerning antimicrobial use and resistance. *Arch Intern Med* 2004;164:1451–1456.
2. Davey P G, Parker S E, Orange G, Malek M, Dodd T. Prospective audit costs and outcome of aminoglycoside treatment and of therapy for Gram-negative bacteraemia. *J Antimicrob Chemother* 1995;36:561–575.
3. Dunagan W C, Woodward R S, Medoff G, et al. Antibiotic misuse in two clinical situations: Positive blood cultures and administration of aminoglycosides. *Rev Infect Dis* 1991;13:405–412.
4. Seaton RA, Nathwani D. Rationale for sepsis management in immunocompetent adults. *Proc R Coll Physicians Edinburgh* 2000;30:11–19.
5. McLaughlin CM, Bodasing N, Boyter A, Fenelon C, Fox JG, Seaton RA Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: An intervention study. *Q J Med* 2005;98:745–752.
6. Ansari F, Gray K, Nathwani D, et al Outcomes of an intervention to improve hospital antibiotic prescribing: Interrupted time series with segmented regression analysis. *J Antimicrob Chemother*, 2003;52:842–848.
7. Grayson M L, Melvani S, Kirsa S W, et al. Impact of an electronic antibiotic advice and approval system on antibiotic prescribing in an Australian teaching hospital. *Med J Aust* 2004;180:455–458.
8. Fraser GL, Stogsdil P, Dickens JD, et al. Antibiotic optimisation. An evaluation of patient safety and economic outcomes. *Arch Intern Med* 1997;157:1689–1694.
9. Gomez J, Conde Cavero SJ, Hernandez Cardona JL, et al. The influence of the opinion of an infectious disease consultant on the appropriateness of antibiotic treatment in a general hospital. *J Antimicrob Chemother*, 1996;38:309–314.
10. Byl B, Clevenbergh P, Jacobs F, et al. Impact of infectious diseases specialists and microbiological data on the appropriateness of antimicrobial therapy for bacteraemia. *Clin Infect Dis*, 1999;29:60–66.
11. Nathwani D, Davey P, France A J, et al. Impact of an infection consultation service for bacteraemia on clinical management and use of resources. *Q J Med* 1996;89:789–797.
12. Nathwani D and on behalf of Scottish Medicines Consortium (SMC) Short Life Working Group, The Scottish Executive Health Department Healthcare Associated Infection Task Force. Antimicrobial prescribing policy and practice in Scotland: Recommendations for good antimicrobial practice in acute hospitals. *J Antimicrob Chemother* 2006;57:1189–1196.

13. World Health Organisation. ATC index with DDDs. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology, 2003. Available at: www.whocc.no/atcddd
14. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858–873.
15. McCabe WR, Jackson GG. Gram-negative bacteraemia. *Arch Intern Med* 1962;110;92–100.
16. Leibovici L, Shraga I, Drucker M, et al. The benefit of appropriate antimicrobial treatment in patients bloodstream infection. *J Intern Med* 1998;244:379–386.
17. Seaton RA, Nathwani D, Phillips G, et al. Clinical record keeping in patients receiving antibiotics in general medical wards. *Health Bull*, 1999;57:28–33.
18. Meehan TP, Fine MJ, Krumholtz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;278:2080–2084.
19. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 1997;24:796–809.
20. Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003;115:529–535.
21. Sevinc F, Prins JM, Koopmans RP, et al. Early switch from intravenous to oral antibiotics: Guidelines and implementation in a large teaching hospital. *J Antimicrob Chemother*, 1999;43:601–606.
22. Laing RBS, MacKenzie AR, Shaw H, Gould IM, Douglas JG. The effect of intravenous-to-oral switch guidelines on the use of parenteral antimicrobials in medical wards. *J Antimicrob Chemother*, 1998;42:107–11.
23. Chan R, Hemeryck L, O'Regan M, Clancy L, Feely J. Oral versus intravenous antibiotics for community acquired lower respiratory tract infection in a general hospital: Open, randomised controlled trial. *Br Med J* 1995;310:1360–1362.
24. Fowler VG, Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteraemia according to compliance with recommendations of infectious diseases specialists; experience with 244 patients. *Clin Infect Dis* 1998;27:478.
25. Al-Eidan FA, McElnay JC, Scott MG, et al. Use of a treatment protocol in the management of community acquired lower respiratory tract infection. *J Antimicrob Chemother* 2000;45:387–394.
26. Gross R, Morgan AS, Kinky DE, et al. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis*, 2001;33:289–295.
27. White AC, Atmar RL, Wilson J, et al Effects of requiring prior authorisation for selected antimicrobials: Expenditures, susceptibilities and clinical outcomes. *Clin Infect Dis* 1997;25:230–239.
28. MacKenzie FM, Struelens MJ, Towner KJ, Gould IM, on behalf of the ARPAC Steering Group and the ARPAC Consensus Conference Participants. Report of the Consensus Conference on Antibiotic Resistance; Prevention and Control (ARPAC). *Clin Microbiol Infect* 2005;11:938–954.
29. Seto W-H, Ching T-Y, Kou M, et al. Hospital antibiotic prescribing successfully modified by immediate concurrent feedback. *Br J Clin Pharmacd* 1996;41:229–234.
30. Seaton RA, Bell, E, Gourlay Y, Semple L. Nurse-led management of uncomplicated cellulitis in the community; evaluation of a protocol incorporating intravenous ceftriaxone. *J Antimicrob Chemother* 2005;55:764–767.

31. Martinez MJ, Freire A, Castro I, et al Clinical and economic impact of a pharmacist-intervention to promote sequential intravenous to oral clindamycin conversion. *Pharm World Sci* 2000;22:53–58.
32. Skoog G, Cars O, Skarlund K et al. Large scale nationwide point prevalence study of indications for antibiotic use in 54 Swedish hospitals in 2003. Clin Microbiol Inf. 2004; 10 (supp 3): 326
33. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101:1644–1655.
34. British Thoracic Society. Guidelines for the management of community acquired pneumonia in adults. *Thorax* 2001;56 (suppl IV):1–55.
35. Seaton RA, Nathwani D, Burton P, et al. Point prevalence survey of antibiotic use in Scottish hospitals utilising the Glasgow Antimicrobial Audit Tool (GAAT). *Int J Antimicrob Ag* (2007); 29:693–699.
36. Knox K, Lawson W, Dean B, Holmes A Multidisciplinary antimicrobial management and the role of the infectious diseases pharmacist—A UK perspective. *J Hosp Infect* 2003;53:85–90.
37. Dean B, Lawson W, Jacklin A, Rogers T, Azadian B, Holmes A. The use of serial point-prevalence studies to investigate hospital anti-infective prescribing. *Int J Pharm Pract* 2002;10:121–125.
38. Gould IM, Jappy B. Trends in hospital prescribing after introduction of an antibiotic policy. *J Antimicrob Chemother* 1996;38:895–904.
39. Nathwani D, Rubinstein E, Barlow G, Davey P. Do guidelines for community-acquired pneumonia improve the cost-effectiveness of hospital care? *Clin Infect Dis* 2001;32:728–740.

*This page intentionally blank*

# Chapter 6
# Antibiotic Use in Hospitals in the United States SCOPE-MMIT Antimicrobial Surveillance Network

Amy Pakyz and Ron Polk

## Introduction

There are few recent published multihospital analyses of antibiotic use in the United States. This is due to the difficulty in acquiring antibiotic use data, especially in acquiring measures of antibiotic use that are not based on antibiotic purchases but actual consumption (Fridkin et al. 1999, Fridkin and Gaynes 1999, Carling et al. 1999, Centers for Disease Control and Prevention 2003). Measures of antibiotic use based on purchase data are indirect and dependent on purchasing variations, manufacturer drug pricing, and vendor discounts (Madaras-Kelly 2003).

The most recent data regarding antibiotic use in U.S. hospitals come from the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project, a surveillance network begun by the Centers for Disease Control and Prevention's Hospital Infection Program and the Rollins School of Public Health at Emory University (Centers for Disease Control and Prevention 2003). The focus of Project ICARE has been on antimicrobial use and bacterial resistance within the intensive care unit, and not on the hospitalwide demographics of use (Fridkin et al. 2001, 2002a). Project ICARE no longer collects antimicrobial use data, in part because of the extensive time and labor requirements for data collection.

## SCOPE-MMIT Antimicrobial Monitoring Network

The Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE)-MediMedia Information Technology (MMIT) Antimicrobial Surveillance Network (SCOPE-MMIT) has measured antibiotic use in participating hospitals starting in 1999 and was one of the largest electronic surveillance networks of antibiotic use in the United States.

The SCOPE-MMIT Antimicrobial Surveillance Network represented an alliance between SCOPE and MMIT (MediMedia Information Technology, Yardley, PA). SCOPE measured and evaluated nosocomial bloodstream infections

since 1995 (Edmond et al.1999). MMIT was a private company that provided detailed patient-level and aggregate-level analysis of drug use to approximately 70 subscribing U.S. nongovernmental hospitals, and linked drug use to hospital and patient demographics. MMIT obtained permission from its participant hospitals to provide antibiotic use data to SCOPE investigators. The SCOPE-MMIT Antimicrobial Surveillance Network has measured antibiotic use in participating hospitals, beginning with 19 hospitals in 1999 and expanded to include 45 hospitals in 2003. MMIT electronically extracted data from inpatient billing records at each hospital including all drugs dispensed during hospitalization. Drug identity was determined from recognition of codes from the Uniform System of Classification (IMS, Plymouth Meeting, PA). Antibiotic use was identified by recognition of antibacterial drugs (code 15000), antiviral drugs (code 82000), and antifungal drugs (code 38000). Patient-level data were aggregated to provide an analysis of hospitalwide antimicrobial use.

## Measurement of Antibiotic Use

The defined daily dose per 1000 patient days (DDD/1000PD) was calculated for each antibiotic based on inpatient billing data at each hospital using the WHO Collaborating Centre for Drug Statistics Methodology (Cosentino et al. 2000; World Health Organization Collaborating Centre for Drug Statistics Methodology).

## Hospital and Patient Demographics

The demographics for 37 hospitals participating in SCOPE-MMIT for the year 2002 are summarized in Table 6.1. All hospitals are general medical-surgical hospitals. Hospitals that are members of the Council of Teaching Hospitals and Health Systems (The Association of American Medical Colleges, www.aamc.org) were designated as teaching hospitals; ten hospitals were teaching hospitals. Twenty of the hospitals were located in the Northeast, thirteen in the South, three in the West, and one in the Midwestern U.S.

## Antimicrobial Use

A total of 688,166 patients were admitted to these 37 hospitals during year 2002. Of those admitted, 376,120 patients (55%) received at least one dose of a systemic antibiotic during hospitalization (interhospital range = 36% to 67%). Cefazolin was used most frequently and was given to 32% of patients who received any antibiotic and to 18% of all admissions (Table 6.2). Levofloxacin was administered to 20% of patients who received an antibiotic, and to 11% of all admissions. On average, more patients received a single dose of an antibiotic (~15%) than any other number of doses (Table 6.3), and most patients received

TABLE 6.1. Demographics for 37 hospitals during year 2002 that participated in the SCOPE-MMIT network

| Characteristic | Mean ± SD | Median (range) |
|---|---|---|
| Admissions | 18,351 + 12,011 | 14,720 (1820–40,676) |
| Patient days | 92,271 ± 65,830 | 74, 848 (11, 309–219, 634) |
| Average length of stay (days) | 4.97 ± 0.76 | 4.95 (3.69–6.71) |
| Staffed beds | 349 ± 211 | 301 (62–778) |
| Occupied beds | 238 ± 154 | 174 (31–562) |
| ICU beds | 21 ± 17 | 16 (0–80) |
| Medicare case mix index | 1.49 ± 0.25 | 1.49 (0.94–2.0) |
| Number of surgeries/1000 admissions | 353 ± 229 | 286 (37–1150) |
| Infection-related ICD-9 codes/1000 admissions | 38.7 ± 14.7 | 36.8 (16.7–79.9) |
| Age | 53.2 ± 5.4 | 53.9 (41.2–65.2) |

only a few doses of any given antibiotic. For drugs that are typically used for surgical prophylaxis (e.g., cefazolin) or those that are relatively toxic (e.g., gentamicin), receipt of only a few doses would seem appropriate. For other drugs, such as the fluoroquinolones, levofloxacin and ciprofloxacin, the reasons are less obvious. The average number of doses given for each of the 10 most frequently prescribed antibiotics was generally 4–6, though the average number of doses of clindamycin was 10. After 10 doses of the most frequently prescribed drugs are given, approximately 70–90% of all doses will have been given (Table 6.3), though there is variability depending on the number of doses typically administered each day.

There were 32 hospitals that provided at least 3 years of antibiotic use between 1999 through 2002. The year-to-year intrahospital variability in total antimicrobial drug use was relatively small (CV = 11.3%). In contrast, the interhospital

TABLE 6.2. The 10 most frequently prescribed antibacterial drugs expressed as a proportion of patients who received any antibacterial drug (mean, median, minimum, and maximum) and as a mean percentage of the total patient census, and the average number of doses received by each patient

| Rank/antibacterial | Mean | Median | Min | Max | Proportion of total patient census | Ave. No. of doses |
|---|---|---|---|---|---|---|
| 1. Cefazolin | 32% | 31% | 6% | 47% | 18% | 6 |
| 2. Levofloxacin | 20% | 22% | 0% | 54% | 11% | 5 |
| 3. Ceftriaxone | 13% | 14% | 1% | 37% | 7% | 5 |
| 4. Vancomycin | 13% | 10% | 1% | 25% | 7% | 8 |
| 5. Ampicillin | 8.8% | 6% | 0.01% | 51% | 5% | 7 |
| 6. Gentamicin | 8.5% | 7% | 0% | 25% | 5% | 6 |
| 7. Ciprofloxacin | 7.3% | 8% | 0.01% | 21% | 4% | 8 |
| 8. Metronidazole | 7.0% | 6% | 0.6% | 15% | 4% | 4 |
| 9. Azithromycin | 6.0% | 6% | 0% | 16% | 3% | 5 |
| 10. Clindamycin | 6.0% | 5% | 1% | 10% | 3% | 10 |

TABLE 6.3. The proportion of patients (%) who received the indicated number of doses for the most commonly used antibacterial drugs

| Antibiotic | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cefazolin | 20 | 12 | 11 | 12 | 7 | 6.7 | 5.8 | 4.3 | 3 | 2.5 | 85 |
| Levofloxacin | 15 | 15 | 14 | 12 | 10 | 7.5 | 6.0 | 4.6 | 3 | 2.5 | 89 |
| Ceftriaxone | 21 | 15 | 14 | 12 | 8.7 | 6.7 | 4.7 | 4.0 | 3 | 2 | 90 |
| Vancomycin | 21 | 13 | 9 | 8 | 6.5 | 5.5 | 4.0 | 4.0 | 3 | 2.6 | 77 |
| Ampicillin | 5 | 4 | 2 | 3.5 | 2 | 2.4 | 2.0 | 2 | 0.9 | 0.7 | 25 |
| Gentamicin | 26 | 16 | 11 | 9.1 | 6.7 | 5.7 | 3.7 | 3.9 | 2.3 | 2.3 | 86 |
| Ciprofloxacin | 10 | 10 | 9.7 | 10 | 8.1 | 8.4 | 6.2 | 5. | 4 | 4 | 76 |
| Metronidazole | 3 | 2 | 1.7 | 2 | 2 | 2.2 | 2.0 | 1.6 | 1.6 | 1.1 | 19 |
| Azithromycin | 13 | 16 | 13 | 15 | 11 | 9.5 | 5.5 | 4.8 | 2.9 | 2.6 | 93 |
| Clindamycin | 15 | 7.1 | 7.6 | 7.2 | 6.1 | 6.3 | 5.0 | 5 | 4.4 | 3.6 | 67 |

variability in total antibiotic use during year 2002 was much larger (599 ± 161 DDD/1000PD, CV = 27%, range = 226 to 923 DDD/1000PD; Figure 6.1). On average, the majority of antibiotic use is comprised of first- and third-generation cephalosporins (13 and 12% of total antibacterial use, respectively), β-lactam/β-lactamase inhibitor combinations (18% of total), and fluoroquinolones (24% of total), Figure 6.2. However, there is marked variability of use within a given class, in part reflecting formulary decisions at individual hospitals. Drugs for which there is only one member of the class, such as vancomycin (Figure 6.3), are also

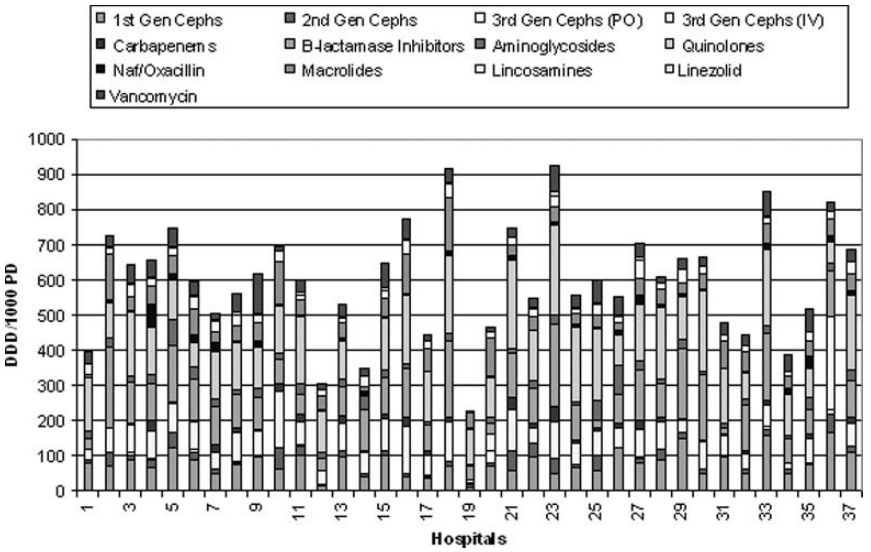



FIGURE 6.1. Summary of antibacterial drug use of 13 classes measured by Defined Daily Dose per 1000 patient-days (DDD/1000PD) in 37 hospitals that participate in the SCOPE-MMIT Antimicrobial Monitoring Network.

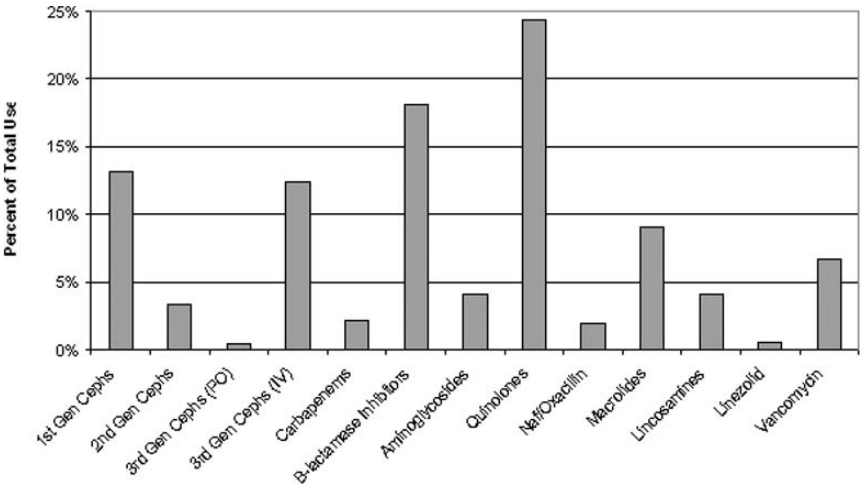



FIGURE 6.2. Summary of antibacterial drug use of 13 classes measured by percent of total use of antibacterials in 37 hospitals that participate in the SCOPE-MMIT Antimicrobial Monitoring Network.

noteworthy for variability in use. Figures 6.4 and 6.5 respectively show the variability in use of fluoroquinolones and potent β-lactams.

## Antimicrobial Restriction Policies

Antimicrobial use at each hospital may, in part, be influenced by hospital policy to restrict or otherwise influence use. Questionnaires were mailed to each director

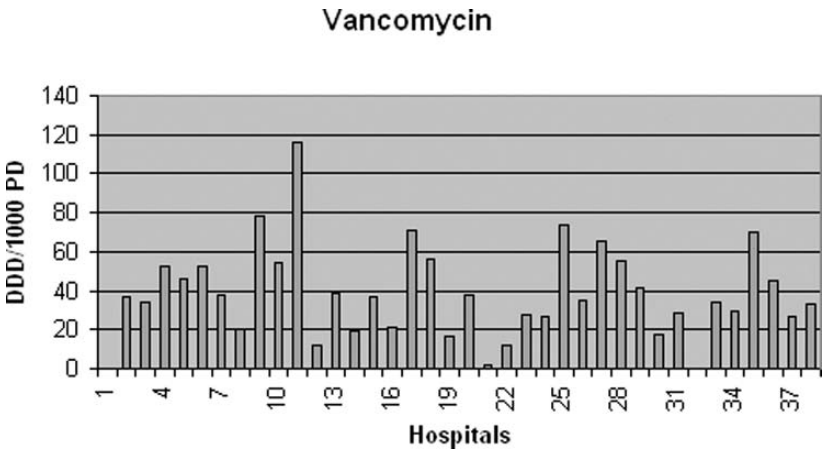



FIGURE 6.3. Summary of vancomycin use measured by Defined Daily Dose per 1000 patient-days (DDD/1000PD) in 37 hospitals that participate in the SCOPE-MMIT Antimicrobial Monitoring Network.

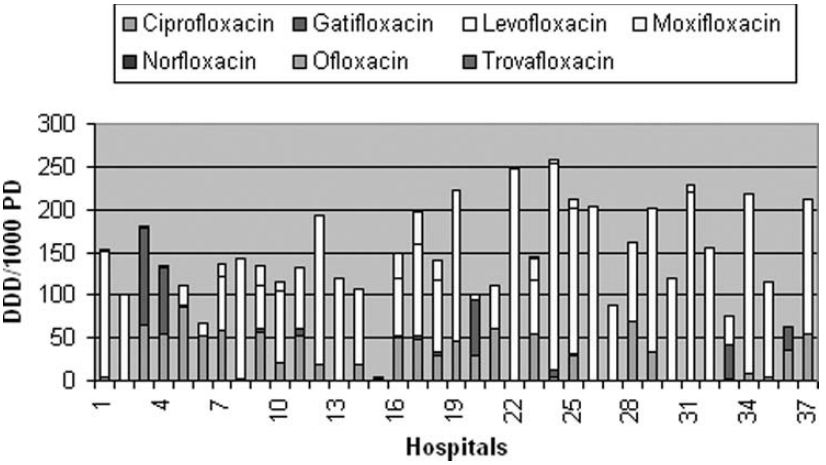



FIGURE 6.4. Summary of fluoroquinolone class use measured by Defined Daily Dose per 1000 patient-days (DDD/1000PD) in 37 hospitals that participate in the SCOPE-MMIT Antimicrobial Monitoring Network.

of pharmacy to determine activities that may have influenced the use of antimicrobial drugs. The questionnaire attempted to determined policy toward antibiotic restriction(s), selective reporting of antimicrobial susceptibility test results, need for required approval for select antimicrobials, intravenous (IV)-to-oral (PO) "switch" programs, and the presence of "cycling" programs. Twenty-five completed questionnaires were returned and 24 hospitals reported that an effort was

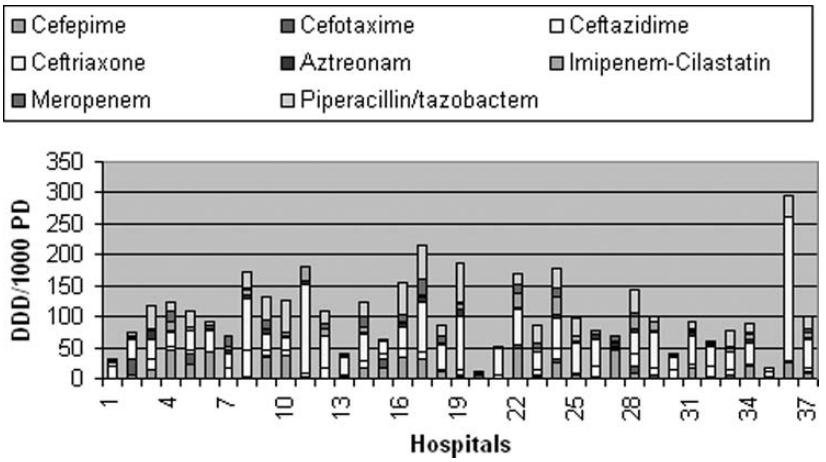



FIGURE 6.5. Summary of potent beta-lactam use measured by Defined Daily Dose per 1000 patient-days (DDD/1000PD) in 37 hospitals that participate in the SCOPE-MMIT Antimicrobial Monitoring Network.

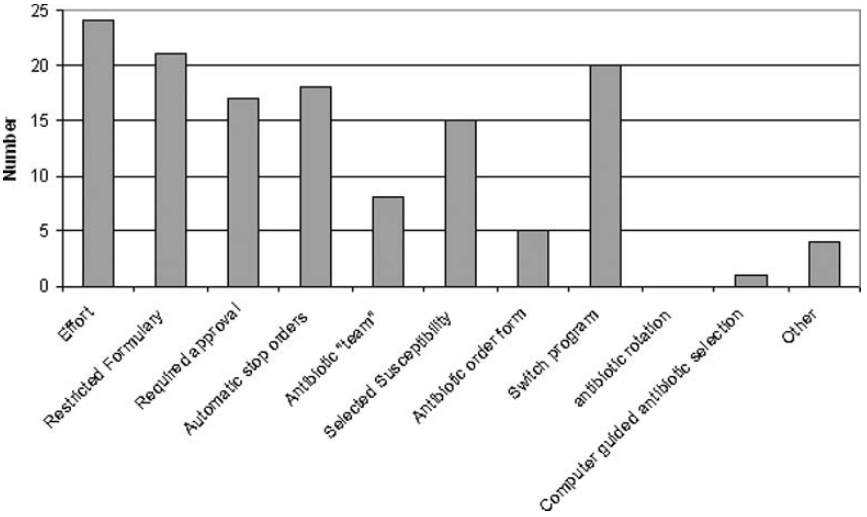



FIGURE 6.6. Summary of antibiotic control policies for 25 SCOPE-MMIT hospitals.

made to restrict or otherwise impact on antibiotic use (Figure 6.6). The most commonly employed management strategies included a restricted formulary (84%), IV to PO "switch" program (80%), automatic stop orders (72%) and required approval for restricted drugs (68%). No hospital used antibiotic cycling as a strategy, and only one hospital used computer guided antimicrobial selection to influence antimicrobial therapy.

## Antibiotic Costs

When costs of antimicrobials were normalized to patient census, the mean cost of antimicrobials/admission was $66.51 (range = $7.20–$148.40), and the mean cost/patient day was $13.29 (range = $3.47–$26.50). When antibiotic costs were normalized for only the proportion of patients who actually received antibiotics, the mean cost of antimicrobials/admission was $116.65 (range = $14.93–$240).

## Conclusion

The types of antibiotics used in U.S. hospitals are very different today versus 1960 through 1980 when tetracyclines, first generation cephalosporins, aminoglycosides, and chloramphenicol were commonly used. Despite the current widespread use of cefazolin, commonly used antimicrobials are more likely to be more broad-spectrum bactericidal drugs, such as the third- and fourth-generation cephalosporins, β-lactam/β-lactamase inhibitors, and fluoroqinolones. Resistance

among nosocomial pathogens continues to increase and undoubtedly reflects the widespread use of these potent drugs, both in the hospital and the surrounding community (Fridkin et al. 1999, 2002b, Fridkin and Gaynes 1999, National Nosocomial Infections Surveillance System Report 2001, Centers for Disease Control and Prevention 2003, Neuhauser et al. 2003). In particular, rates of fluoroquinolone resistance in nosocomial pathogens such as *E. coli* and *P. aeruginosa* are increasing rapidly; this may reflect the relatively heavy use in the hospital as well as in the community (Polk et al. 2004).

The SCOPE-MMIT Antimicrobial Monitoring Network disbanded in 2004 due to the time and resources required to maintain the network. Currently there are newer databases available which are providing antimicrobial usage data including a consortium of academic teaching hospitals, the University HealthSystem Consortium, and a consortium of smaller, community medical-surgical member hospitals of Solucient, LLC. Investigations generated from these databases will continue to provide hospitalwide demographic antimicrobial usage data from U.S. hospitals(Polk et al. 2007).

## *References*

Carling PC, Fung T, Coldiron JS (1999) Parenteral antibiotic use in acute-care hospitals: A standardized analysis of fourteen institutions. Clin Infect Dis 29:1189–1196.

Centers for Disease Control and Prevention (2003) National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 31:481–498.

Cosentino M, Leoni O, Banfi F, Lecchini S, Frigo, G (2000) An approach for the estimation of drug prescribing using the defined daily dose methodology and drug dispensation data. Theoretical considerations and practical applications. Eur J Clin Pharmacol 56:513–517.

Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP (1999) Nosocomial bloodstream inflections in United States hospitals: A three-year analysis. Clin Infect Dis 29:239–344.

Fridkin SK, Gaynes RP (1999) Antimicrobial resistance in intensive care units. Clin Chest Med 20:303–316.

Fridkin SK, Steward CD, Edwards JR, Pryor ER, McGowan JE Jr, Archibald LK, Gaynor RP, Tenover FC (1999) Surveillance of antimicrobial use and antimicrobial resistance in United States hospitals: Project ICARE phase 2. Project Intensive Care Antimicrobial Resistance Epidemiology (ICARE) hospitals. Clin Infect Dis 29:245–252.

Fridkin SK, Edwards JR, Courval JM, Hill H, Tenover FC, Lawton R, Gaynes RP, McGowan JE Jr (2001) The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. Ann Intern Med 135:175–183.

Fridkin SK, Lawton R, Edwards JR, Tenover FC, McGowan JE, Gaynes RP, and the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project, and the National Nosocomial Infections Surveillance (NNIS) System Hospitals (2002a) Monitoring antimicrobial use and resistance: Comparison with a national benchmark on reducing vancomycin use and vancomycin-resistant enterococci. Emerg Infect Dis 8:702–707.

Fridkin SK, Hill HA, Volkova NV, Edwards JR, Lawton RH, Gaynes RP, McGowan JE Jr (2002b) Temporal changes in prevalence of antimicrobial resistance in 23 US hospitals. Emerg Infect Dis 8:697–701.

Madaras-Kelly K (2003) Optimizing antibiotic use in hospitals: The role of population-based surveillance in limiting antibiotic resistance. Pharmacother 23:1627–1633.

National Nosocomial Infections Surveillance (NNIS) System Report (2001), data summary from January 1992–June 2001, Issued August 2001. Am J Infect Control 29:404–421.

Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP (2003) Antibiotic resistance among gram-negative bacilli in US intensive care units: Implications for fluoroquinolone use. JAMA 289:885–888.

Polk RE, Johnson CK, McClish D, Wenzel RP, Edmond MB (2004) Predicting hospital rates of fluoroquinolone-resistant *Pseudomonas aeruginosa* from fluoroquinolone use in US hospitals and their surrounding communities. Clin Infect Dis 39:497–503.

Polk RE, Letcavage J, Mahoney A, MacDougall C (2007) Adult Antibiotic Usage in 131 US hospitals: Comparison of Defined Daily Dose(DDD) to Duration of Therapy (DOT)/1000 patient days (PD). Clin Infect Dis 44:664–670.

World Health Organization Collaborating Centre for Drug Statistics Methodology http://www.whocc.no/atcddd/.

*This page intentionally blank*

# Chapter 7
# New Hospital Initiatives in Fighting Resistance

Fiona Cooke and Alison Holmes

## Summary

The fight against the emergence and spread of antibiotic resistant organisms in hospitals demands a wide-ranging and comprehensive strategy of attack. Although a multifaceted approach is required, the following discussion will be restricted to the translation of new molecular techniques into diagnostic tests, and initiatives to optimize antibiotic prescribing in hospitals. An ideal rapid test would determine categorically whether a pathogen is present or not in a clinical sample, and if so, the identification and antibiotic susceptibility, all within 1–2 hours. Widespread use of such tests, and their translation into portable "near patient tests," will undoubtedly have significant consequences regarding patient management and control of antibiotic resistance. In the wider hospital setting, developments in information technology and new applications of management, organization, and service delivery must be adopted to optimize antibiotic prescribing. By combining timely diagnostics with the larger-scale hospital systems for the delivery of care, we may start to win the battle against antibiotic resistance.

## Introduction

When a patient is suspected of having an infection, a number of key questions are considered (Box 7.1). In this chapter, the relevance of each decision-making point in terms of control of resistance at the patient and population level will be discussed in turn. In general, emphasis will be on bacterial infections and use of antibiotics, rather than viral or fungal conditions, although many concepts are equally applicable. Focus will be on the hospital situation rather than the community, although the division between "hospital" and "community" is becoming more blurred. Furthermore, resistant organisms and resistance genes do not respect this rather artificial boundary, and exist as a dynamic population, continually transferring between different environments and hosts.

Box 7.1. Key Questions / Decision-Making Points

These are considered when a patient is suspected of having an infection. Their relevance to reducing antibiotic resistance will be discussed in this chapter.

- Does this patient have any microbiological evidence of an infection?
- If so, what is the identification of the organism(s)?
- What is the antibiotic susceptibility pattern?
- Does the organism possess certain virulence factors?
- How can antibiotic prescribing be optimized at the prescriber and the hospital level?

To begin to control the spread of resistant organisms, and discourage the development of new resistance patterns, a multifaceted approach is required, starting down at the level of the genome and working up to the individual prescriber and the organizational framework and culture in which they work.

## Microbiological Evidence of Infection

Traditionally, microbiological evidence of infection may be thought of as whether an organism can be cultured from a normally sterile site. Culturing an organism is slow and identification tests are often time-consuming, so nucleic-acid based tests have been considered as an alternative. Unfortunately, the presence or absence of bacterial DNA in a clinical sample is more difficult to interpret, and evidence that the patient has an infection may be more contentious.

Ideally, a molecular test would confirm or refute the presence of bacterial DNA in a clinical sample, and possibly identify the organism, within 2 hours of taking the sample (Boissinot and Bergeron 2002). These DNA-based tests have numerous advantages over culture: they circumvent the inherent delay with slow-growing or fastidious organisms; they should detect unculturable organisms such as *Tropheryma whippelii* and *Treponema pallidum*; they can potentially quantify the bacterial load (in a manner similar to HIV and HCV viral loads); and bacterial DNA should be present even if the patient has received antibiotics. However, one of the greatest difficulties is differentiating between the presence of any bacterial DNA (which may arise from dead or degraded bacteria) and living bacteria. In addition, "background" bacterial DNA is known to be present in blood of patients without a true bacteremia and even in healthy individuals (Nikkari et al. 2001). There is also the risk of laboratory contamination. Some tests can identify the pathogen, e.g., using 16 S rRNA as discussed later, but most current techniques struggle to provide susceptibility data. However, identification of the pathogen alone may direct the prescriber toward relevant local epidemiological data, while waiting for full susceptibility results once the organism has grown.

The level of sensitivity required for DNA-based tests varies with different clinical samples. For example, in the case of CSF, any technique employed should be able to detect a single copy of the genome of any microorganism. However, this level of sensitivity would probably be too extreme for urine samples, although urine is also normally sterile. For urine samples, growth of greater than $10^4$ CFU/ml is usually regarded as significant, so the DNA-based test must be adjusted and interpreted accordingly (Boissinot and Bergeron 2002).

As an alternative to DNA-based tests, immunoassays which focus on the host immune response have the potential to rapidly diagnose an infection. New developments include cell-based biosensors, such as a system based on B lymphocytes which had been engineered to emit light within seconds of exposure to specific bacteria and viruses (Rider et al. 2003). While this whole process could theoretically detect responses to specific infectious agents in less than 5 minutes (including sample preparation time), there are concerns regarding specificity (due to cross-reactivity with heterologous antigens), sensitivity (due to microbes showing antigenic variation to evade host defenses), sample preparation, and cell storage (Relman 2003).

## Identification of the Organism(s)

Most diagnostic bacteriology laboratories in the United Kingdom depend on phenotypic techniques to identify organisms, which obviously take time while the organism grows. Laboratories usually aim for a 48-hour turnaround time, from when the specimen is received to issuing a report. More unusual bacteria (or those with less common antibiotic sensitivity patterns) may take longer to identify, and some slow-growing organisms—*Mycobacterium tuberculosis* being an extreme example—will always take more time. Ideally, microbiology identification (and sensitivity) results would be available to the clinician within a time frame similar to biochemistry and hematology results—which in most cases come back within an hour. If this was so, and clinicians had almost immediate access even to the identification of any pathogen(s) present, improvements in individual patient management should significantly decrease costs and reduce both the generation and spread of antibiotic resistant organisms (Box 7.2).

Most rapid tests currently used in bacteriology detect antigens in clinical specimens, such as legionella urinary antigen and streptococcal antigens in CSF, but these are often limited to one species. Molecular tests that have become "routine," such as chlamydia LCR (ligase chain reaction), are usually performed in virology laboratories, which historically have placed greater reliance on molecular techniques. New DNA-based tests for diagnostic laboratories fall into two groups: those that directly detect the organism in the specimen, e.g., pathogen-specific or broad-range polymerase chain reaction (PCR), and those that identify an organism after it has grown, either on a plate or in culture medium [e.g., fluorescent *in situ* hybridization (FISH) or PCR]. All new tests must be thoroughly evaluated to ensure ubiquity (i.e., ability to

Box 7.2. Advantages of Prompt Identification of Organisms and Susceptibility Pattern

- Encourages broad-spectrum antibiotics to be replaced by agents with a narrower spectrum. Narrow-spectrum drugs are often cheaper, less toxic, have fewer side effects, and less disruptive to normal flora. Reduction of selective pressure from broad-spectrum agents may discourage the development of resistance.
- Improves individual patient management by enabling clinicians to be aware of potential problems and complications associated with the identified organism, e.g., metastatic effects of *S. aureus*, necrotizing fasciitis associated with group A streptococcus.
- Early identification of the organism (and its susceptibility) may permit targeting and stopping antibiotics sooner. Prescribing appropriate targeted antibiotic therapy earlier reduces the overall quantity of antibiotics prescribed. In some cases antibiotics may not be required at all, for example if coagulase-negative staphylococci were identified in blood cultures and considered a contaminant.
- Prompt identification of organisms such as *C. difficile* or multiresistant organisms would enable infection control issues to be addressed more readily, and the triage of limited isolation facilities.

detect all strains of the targeted audience) as well as rapidity, sensitivity, and specificity (Boissinot and Bergeron 2002). The rapid evolution of microbes through the exchange of genetic information means that target genes and multiplexing strategies must be chosen carefully.

## *Nucleic Acid Extraction*

The efficient extraction of nucleic acid from organisms in a variety of clinical samples poses many challenges. In general, recovery of DNA depends on the degree of cell lysis, the binding of DNA to particulate material, and degradation or shearing of DNA (Coyne et al. 2004). An optimal extraction method should efficiently lyse bacterial cell walls in Gram-positive bacteria without damaging DNA purified from more fragile Gram-negative bacteria. Isolated nucleic acid should be protected from degradation, and inhibitors of hybridization or amplification should be removed. Operation at an appropriate degree of sensitivity for that sample is imperative, as discussed above. Many current extraction protocols take several hours, require multiple steps or specialized equipment, and are not combined with appropriate sample preparation procedures. Automated fluidic devices that rapidly capture cells and extract, purify, and concentrate the nucleic acid are being developed, and may ultimately encompass amplification and detection steps also (Boissinot and Bergeron 2002).

## *Amplification and Detection of Pathogens*

The first nucleic-acid-based assays which used DNA probe technology were found to have low sensitivity because of the relatively small amounts of starting DNA present in many clinical samples. In the mid-1980s PCR was developed and has since become the most widely used technique for DNA amplification (Yang and Rothman 2004). Other less common amplification techniques include amplification of hybridizing probes (e.g., ligase chain reaction and Q-beta replicase amplification); amplification of signal generated from hybridizing probes (e.g., branched DNA and hybrid capture); and transcription-based amplification (e.g., nucleic-acid-sequence-based amplification and transcription-mediated amplification) (Wolk et al. 2001).

Most broad-range PCRs focus on targets that are exclusive to bacteria such as the16 S rRNA gene, and for diagnostic purposes concentrate on samples from normally-sterile sites. Comparison of product sequence with an electronic database such as RIDOM (Ribosomal Differentiation of Medical Microorganisms at http://ridom-rdna.de/) can potentially identify any organism. Results from some broad-range PCR studies have been promising, such as testing patients at risk of infective endocarditis, febrile children at risk of sepsis, febrile neutropenic cancer patients, and critically ill patients in Intensive Care (Yang and Rothman 2004). However, other studies showed poor specificity, and clinical interpretation of results was difficult (Peters et al. 2004b). Possible targets to identify groups of bacteria, e.g., *rpoB, gyrB*, ITS (Internal Transcribed Spacer region), and *groEL* for mycobacteria species (Kusunoki et al. 1991), may prove useful.

The interpretation of PCR results has always been challenging. High rates of false-positive or false-negative results may arise due to technical issues, sample contamination, lack of specificity or amplification problems. Distinguishing between latent infection and active disease, and also between colonization and infection, is not straightforward. While the techniques per se are not difficult, some processes are more technically demanding to perform and require commitment by individual scientists to learn new skills, with support from management.

Quantitative real-time PCR, which combines amplification and detection in a single reaction tube, is a major breakthrough in molecular diagnostics (Yang and Rothman 2004). The applications of real-time PCR in routine laboratory testing have been comprehensively reviewed (Espy et al. 2006). Real-time PCR is more rapid than conventional PCR as the product can be measured simultaneously with synthesis, using a fluorescence-labeled internal DNA probe [e.g., Taqman; fluorescent resonance energy transfer (FRET); molecular beacon probes] or fluorescent DNA intercalating dyes. One of the major issues is contamination. For example a study of real-time broad-range 16 S rRNA PCR on blood samples from febrile patients found that many PCR products showed unexpected similarity to *Burkholderia* sp. This was later demonstrated to be due to contamination in the commercial DNA isolation kit (Peters et al. 2004a). Contamination risk may be reduced by closed systems, but most real-time PCR processes still need a separate extraction step.

The ability of real-time PCR to quantify nucleic acid is widely exploited in virology (e.g., HIV and HCV viral loads), but there are few published quantitative studies in bacteriology. Hackett et al. demonstrated that real-time PCR for the detection of *Neisseria meningitidis* was highly sensitive, and found that meningococcal DNA load at presentation correlated with disease severity in children (Hackett et al. 2002).

Theoretically, real-time PCR using appropriate primers can look for the presence of any bacteria in clinical samples, such as group A streptococcus (Uhl et al. 2003), group B streptococcus (Uhl et al. 2005), and *Clostridium difficile* (Belanger et al. 2003). Detection of a panel of organisms, for example the causes of community-acquired pneumonia (Morozumi et al. 2006), is often more clinically relevant, and could be extended to include viruses as well as bacteria.

FISH is a promising rapid technique based on hybridizing probes to target rRNA, followed by detection of fluorescence by microscopy. A recent study demonstrated that FISH identified organisms from blood cultures, which had flagged as culture-positive, on average 18 hours faster than conventional techniques (Peters et al. 2006). As the number of probes is increased and the turnaround time reduced, FISH may find a place in some diagnostic laboratories.

## *Genomics*

Since the publication of the *Haemophilus influenzae* genome more than a decade ago (Fleischmann et al. 1995), almost 300 complete bacterial genomes have been sequenced and approximately 950 bacterial sequencing projects are under way (http://www.genomesonline.org/ accessed 04/24/06). Interrogation of microbial genomes provides a wealth of information, including targets to design assays for organism identification and antimicrobial resistance, as witnessed by the ever-increasing numbers of commercially available and "in-house" PCR tests. The genomics revolution has fueled microarray technology, which has a plethora of applications, including organism identification and detection of antibiotic resistance genes, as discussed later.

The sequence of one isolate is not necessarily representative of the species, so there is now a trend toward "comparative genomics" whereby several isolates of one species are sequenced and compared with each other. For example, seven sequences of *Staphylococcus aureus* are publicly available, including hospital- and community-acquired MRSA (Diep et al. 2006) and a vancomycin intermediate-level resistant MRSA isolate from Japan (Kuroda et al. 2001). This approach enables comparison between sequence and phenotypic characteristics, particularly for virulence traits and antibiotic resistance, and may ultimately help discover ways to prevent new resistance arising and to find susceptibility in already resistant pathogens.

## *Proteomics*

Proteomics involves the interpretation of protein expression patterns, and provides a novel way of looking at clinical specimens for evidence of infection. Proteomic

fingerprinting is based on the underlying premise that infectious diseases are associated with distinct combinations of biomarkers. MALDI-TOF (matrix-assisted laser desorption-ionization time-of-flight) or SELDI-TOF (surface-enhanced laser desorption-ionization time-of-flight) and mass spectrometry have been successfully employed to detect African trypanosomiasis in Kenya (Agranoff et al. 2005). Rather than translate directly into a diagnostic laboratory test, this technique is more likely to help discover novel biomarkers that could be incorporated into simple, affordable tests.

## Antibiotic Susceptibility Pattern of the Organism(s)

For historical reasons, most U.K. bacteriology laboratories determine the phenotypic susceptibility pattern of an organism, which is important in terms of individual patient management. However, it can be argued that at the population level the genotypic pattern is more relevant. It is the presence or absence of resistance genes, and not whether they are expressed, that is significant in terms of spread. Of additional importance is the context of these genes, in that those contained within integrons or harbored by plasmids or mobile genetic elements have greater potential to spread to other organisms.

The rapid latex agglutination test for *mecA*, encoding methicillin resistance, can only be used once *S. aureus* has been cultured. Many other molecular tests for antibiotic resistance genes, such as PCR and FISH, also rely on the cultured organism. However, to provide sensitivity results within the goal of 1–2 hours, direct analysis of clinical samples is imperative. The large number of resistance genes potentially involved limits the application of some techniques, for example real-time PCR can only detect a certain number of fluorophores simultaneously. Theoretically, DNA microarrays, genome-scanning approaches, rapid sequencing methods, and whole-genome amplification techniques could detect the required number of resistance genes. These have limitations, such as the detection of single nucleotide polymorphisms (SNPs) by some microarrays, but the biggest hurdles are the cost and technology, which are prohibitive to most diagnostic laboratories. We welcome initiatives to translate the technology into routine practical tests.

### *MRSA*

Considerable progress has been made with molecular tests for the prompt detection of MRSA. Previously, most methods relied on detecting an *S. aureus* specific gene and *mecA*. However, clinical specimens such as nose swabs usually harbor a range of organisms, including mixed coagulase negative staphylococci (CNS) which may harbor *mecA*, so tests must be able to differentiate between MRSA and methicillin-resistant CNS. By designing oligonucleotides to target MRSA-specific chromosomal sequences, a Canadian group has developed a real-time PCR to discriminate MRSA from methicillin-resistant CNS. Combining this with a rapid DNA extraction method enabled detection of MRSA carriage in less than

1 hour (Huletsky et al. 2004). Compared to traditional laboratory methods for detecting MRSA in nasal swabs, the specificity of their PCR was 98.4%, the positive predictive value was 95.3%, and the sensitivity and negative predictive value were both 100% (Huletsky et al. 2005). A commercial version of this test (Infectio Diagnostic, http://www.geneohm.com) has been approved in North America, and will soon be marketed in Europe. If introduced into microbiology laboratories, this test should facilitate MRSA screening programs, which have been shown to effectively control the spread of MRSA in hospitals with a low prevalence or endemic levels (Cooper et al. 2003). MRSA isolates can be analyzed further with more complex epidemiological typing techniques such as staphylococcal interspersed repeat unit typing (Hardy et al. 2006).

## *Other Resistant Organisms*

As with the identification of organisms, it should be possible to detect any known resistance gene by PCR. Tests in common usage in reference laboratories include PCR for *rpoB* mutations signifying rifampicin resistance in *M. tuberculosis*. Published studies on real-time PCR in bacteriology have recently been reviewed (Espy et al. 2006) and include detection of fluoroquinolone resistance in *S. aureus* due to *grlA* mutations (Lapierre et al. 2003) and prediction of decreased penicillin susceptibility in *N. meningitidis* (Stefanelli et al. 2003). The impact of these rapid results needs continual evaluation: in one study, a PCR-based test for VRE in rectal specimens during a hospital outbreak resulted in complete elimination of VRE transmission (Roger et al. 2001).

## *Local Knowledge of the Epidemiology of Resistance*

More detailed epidemiological information to discriminate between resistant isolates may be gleaned from methods such as restriction fragment length polymorphism (RFLP), pulsed field gel electrophoresis (PFGE), rapid amplified polymorphic DNA (RAPD), microarrays, and multi-locus sequence typing (MLST). Only by detailed analysis of antibiotic resistance genes and their context, and by investigating how they spread both within and between species, can we begin to understand the complex, dynamic nature of the "population" of resistance genes and try to tackle the problem of antibiotic resistance (Bergeron and Ouellette 1998).

Microarrays consist of thousands of nucleic acid targets immobilized on a solid substrate such as a glass slide or silicon wafer. Fluorescently labeled probes made from nucleic acids in a test sample are hybridized to these targets, allowing analysis of relative concentrations of DNA or mRNA in a sample. Microarrays have many applications in infectious diseases (Bryant et al. 2004), such as the construction of an antibiotic resistance array, which exploits the ability to simultaneously analyze thousands of genes (Call et al. 2003). This is more manageable for Gram-positive bacteria rather than the Enterobacteriaceae, due to numbers of genes involved. While microarray technology brings many advantages, it must be remembered that "you only get what you look for", i.e., only target features represented on the slide can be detected.

Thus, the "absence" or "divergence" of a resistance gene (or a class of genes) by microarray does not always mean that the organism is sensitive to that antibiotic. For example, the organism may acquire a resistance gene not represented on the array, or a new resistance mechanism may emerge. Similarly, detection of a resistance gene by a DNA-based array does not preclude the use of that agent in the patient, as the gene may not be expressed. In terms of the global epidemiology of resistance, it is the presence of the gene, its context and potential for transmission that matter.

MLST (Maiden et al. 1998) is more suited to investigating bacterial phylogeny and evolution of population lineages, but can be used for typing outbreaks. Other sequence-based techniques, such as F-AFLP (fluorescence amplified fragment length polymorphism) (Mortimer and Arnold 2001), may direct the development of other diagnostic tests, rather than be used routinely.

The term *molecular theranostics* has been coined to describe the "emerging concept in which molecular biology tools are used to provide rapid and accurate diagnostic assays to enable better initial management of patients and more efficient use of antimicrobials" (Picard and Bergeron 2002). While we can anticipate the advantages that molecular theranostics will bring, careful research on the impact of each technique at many levels will be critical. Unfortunately, the transition of molecular techniques from the research laboratory into the clinical setting is proving difficult. Yet further work is required to translate the science into useful, practical tests that actually change patient management. Only then can we fully address the adage "from bench to bedside."

## Identification of Virulence Factors

While this is not directly related to reducing antibiotic resistance, timely identification of virulence factors or certain serotypes would direct patient management and the use of isolation facilities. Examples include molecular tests to differentiate serotypes such as *E. coli* 0157, toxin producing strains such as Panton-Valentine leucocidin-positive *S. aureus*, and ribotypes such as *C. difficile* 027.

Near Patient Testing

The concept of a "lab-in-a-tube" or "lab-on-a-chip" requires assembly of all steps involved in an assay (probably in a miniaturized format) into one portable device, so the physician can identify the pathogen(s) and resistance profile at the bedside. A variety of methods will probably be involved, including real-time PCR, probe-based assays, bioluminescence real-time amplification, and microarray or micropump technology (Holland and Kiechle 2005). The widespread availability of such near-patient devices, especially in developing countries where diagnostic facilities may be limited, is likely to lead to more appropriate evidence-based treatment and reduce the emergence of new resistant strains. This technology may also find a niche in developed countries with the increasing centralization of diagnostic laboratories and the lack of on-site facilities in many hospitals.

## Optimization of Local Prescribing Behavior

Once the clinical diagnosis of infection is made or suspected, or the need for antibiotic prophylaxis for surgery identified, the hospital prescriber must select which antibiotic(s) to prescribe. There is an overwhelming plethora of guidelines and policies on prescribing antibiotics available in hospitals. However, their actual implementation at the bedside requires new approaches, which deal with both the starting, and the stopping, of antibiotics. These initiatives must consider the working environment, local logistics, the cultural context of prescribing, interprofessional and cross specialty working, clinical roles and accountability, the level of organizational understanding, senior management support, and the clinical role models and leadership. A systems-based approach is required to ensure a hospital can deliver and monitor a program of antibiotic stewardship, beyond having a highly efficient microbiology laboratory that delivers a first class modern service. This systems-based, strategic approach requires chief executive backing (Goldmann et al. 1996), with strong clinical and managerial leadership, and a framework to monitor the implementation and the outcomes. In the absence of this comprehensive approach, institutes are left to rely on the energy and enthusiasm of a few committed individuals, which is inefficient and unsustainable. An organizational framework is required to harness this expertise and maximize its influence and effectiveness, and to provide a sustainable improvement program in antibiotic management. Such a program would be greatly facilitated by information technology and communication and surveillance systems supporting hospital epidemiology and antibiotic prescribing. These would range from real-time detailed local analysis of the changing epidemiology of bacteria, antibiotic resistance and prescribing patterns, links between hospital information systems so data can be analyzed by different denominators and a variety of associations examined, feedback mechanisms and electronic learning with local data, the widespread utilization of barcode technology, electronic prescribing and electronic and robotic dispensing, and the use of trigger systems for automatic review and intervention. In the remainder of the chapter we will address some of the organizational issues for hospitals and not expand further on technological and logistic initiatives.

### *Initiatives to Support and Influence the Prescriber*

The antibiotic choice must ensure coverage of the relevant bacteria, ideally with as narrow a spectrum of activity as possible to minimize exposure and reduce the potential for the emergence of resistance. Each prescriber needs to manage the patient's individual infection circumstance, and also address the public health implications of antibiotic prescribing, and understand and acknowledge this tension (Foster and Grundmann 2006). Antibiotic control is a key component of a hospital's infection control strategy (Anon 2003, 2004), and clinicians must have an understanding of the risks associated with antibiotic prescribing, not just at the initiation of a prescription but also on every subsequent continuing dose. Methods to optimize and control antibiotic selection and initiation are widely addressed,

including electronic and administrative methods, education and awareness, media and communications techniques, restrictive form filling, educational approaches and prompts, computer assisted decision support, reserved policies, Infectious Diseases consults and pharmacists involvement. Some of these are described in other chapters, and those that have been appropriately researched are assessed in a recent Cochrane review (Davey et al. 2006). However, methods to ensure the stopping of an unnecessary prescribed antibiotic once started for treatment purposes (Lambert 1999) are less well addressed. Automatic stop dates, time-limited prescriptions, and dispensing and approval requirements are some of the administrative methods which aim to make it more difficult for prescribers to continue antibiotics for prolonged periods. But many clinicians find it hard to de-escalate or discontinue antibiotic therapy once initiated. The input of specialist clinical expertise to help clinicians safely avoid prolonged and unnecessary antibiotic courses and improve clinical outcome is important, and has been demonstrated to be especially valuable in the ITU setting (Corona et al. 2003). The critical care environment is at the most risk of intense antibiotic use and pressure, and the patients are especially vulnerable.

Further work needs to be done on systems to improve the deescalation and discontinuation of antibiotics, and to reduce some of the commonly used but potentially unnecessarily long treatment courses. One initiative, discussed further in the next section, which could address this issue at the bedside is the application of an "antibiotic care bundle."

Hospitals, and the specialist clinical groups within them, need to ensure that specialist infection expertise is used, and multidisciplinary input fostered. Infection experts also need to understand the knowledge and experience of infection by other specialist services, as well as the context, roles, and behaviors. This understanding will help to develop a more successful influence on antibiotic practice and clinical outcome. The infection experts then can adopt methods that would be the most successful with these different groups. Together, they should set appropriate short-term and long-term goals, and acknowledge the elements of anthropology and behavioral science required (Pulcini et al. 2006).

## *Methods to Standardize Prescribing Practice in Hospitals*

A greater understanding of delivering safety in healthcare and the rapidly changing junior medical work force has contributed to the acceptance that standardized practice, for specific aspects of clinical care, is critical. Standardizing practice may be seen by some consultants as a threat to their autonomy and undermining their clinical skills. But this is not the case when it is clearly seen to be based on best evidence, developed by clinical peers, validated, and the central theme is improved clinical outcomes rather than management targets. With clinician involvement, understanding and ownership of standardized packages of care can be successfully used to minimize risk and optimize the quality of clinical care provided (Edwards et al. 2002, Silversin and Tampa 2000).

Multidisciplinary integrated care pathways (ICPs) are well developed for specific procedures and can cover the patient's pathway from preadmission clinic to postoperative follow-up. These are particularly useful for straightforward surgical admissions, and ensure all required steps are taken and signed off by all of the different members of the multidisciplinary team involved. Antibiotic prescribing, including specific guidance and the standardized recommended prescription, can also be embedded within these ICPs.

The "care bundle" approach is being widely adopted as a method to optimize process delivery in healthcare, as evidenced by the Institute for Healthcare Improvement 100,000 lives campaign in the USA (http://www.ihi.org/IHI/Programs/Campaign/ accessed 05/08/06), the Department of Health Saving Lives programme in the United Kingdom (http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/HealthcareAcquiredInfection/HealthcareAcquiredGeneralInformation/SavingLivesDeliveryProgramme/fs/en), and critical care networks. Care bundles consist of a group of evidence-based actions, instituted over a specific timeframe, which if delivered together have a greater clinical impact than if each element was instituted individually. Care bundles have been developed for critical care, ventilator associated pneumonia, invasive procedures, and the prevention of surgical site infection. We propose that the care bundle method could provide a valuable approach to prescribing antibiotics.

For care bundles to succeed, the science behind each component must be so well established that they are considered standard of care. Bundles must be user-friendly, and ideally consist of between three and five simple, rigorous checkpoints that require yes/no answers. Accountability needs to be clear, and adherence to each point should be measurable. Documentation may be paper-based, for example stickers or stamps in the patient casenotes or paper-forms to be inserted, or documented electronically (where available). In the case of the antibiotic care bundle, electronic records could link directly into prescribing and hospital epidemiology databases which include resistance patterns, and potentially decision support systems (Evans et al. 1998, Sintchenko et al. 2005).

Overall a care bundle should be a cohesive unit, ensuring all steps of care are reliably delivered. Day-to-day clinical practice regarding antibiotic prescribing is often piecemeal in approach in terms of both care delivery and documentation, but the bundle approach would ensure all stages are addressed. The elements of an antibiotic care bundle should build on and crystallize the work of many published studies on optimizing prescribing and its documentation (Seaton et al. 1999). Bundles rely on the mixture of cognitive (education), administrative (recording), and behavioral (feedback of results) methods to achieve quality improvement in care delivery. Auditing compliance will be a useful process measure for performance monitoring of improved healthcare delivery in hospital trusts. Omission of any step in best practice should be regarded as equivalent to committing an error.

An antibiotic care bundle approach could be adopted for both antibiotic treatment Box 7.3 and prophylaxis Box 7.4. Each bundle should be adapted according to local needs and facilities, but all elements of the model must be incorporated, and strategies not found in the bundle should not be added. Bundles could be the pillars of any antibiotic stewardship program, bringing policies and guidelines right to the bedside

Box 7.3. Antibiotic Care Bundle for Prescribing Antibiotics as Treatment in Acute Medical and Surgical Care (Cooke 2007)

We recommend the following points be considered, but each bundle should be adapted according to local needs and facilities:

- Document clinical rationale for antibiotic initiation
- Appropriate specimens sent to microbiology laboratory
- Antibiotic selected according to local policy and risk group (exclude allergy)
- Consider removal of foreign body/drainage of pus/surgical intervention
- Daily review of clinical picture and lab results to consider de-escalation or oral switch or stopping antibiotics
- Antibiotic drug levels monitored as required by local policy

and addressing the fundamental principles of good prescribing practice. Bundles should be reviewed and updated as local epidemiology changes and users report their experiences. Bundles must also incorporate new research and techniques, such as real-time molecular tests to identify pathogens and resistance patterns.

## *Executive Leadership and Management Engagement*

Effective implementation of a sustainable antibiotic stewardship program requires "corporate teeth" and senior support through executive leadership and backing (Goldmann et al. 1996). Through this, a culture that supports and reinforces best practice can be developed. External leverage is a useful tool to drive internal change, and the recognition that a hospital's managing and monitoring of antibiotics is being used as a performance indicator by external bodies such as the Health Care Commission is useful to highlight the need for corporate support in this important area. A corporate understanding that infection control and antibiotic control are interlinked and should be tackled by an integrated strategy was reinforced by the Winning Ways document published in December 2003 by the Department of

Box 7.4. Antibiotic Care Bundle for Prescribing Antibiotics as Surgical Prophylaxis

We recommend the following points be considered, but each bundle should be adapted according to local needs and facilities.

- Agent selected matches local guidelines for that operation for that patient (exclude allergy)
- Timing of first dose is 30min–1 hour preincision
- Stop antibiotics after the pre-operative dose (or first dose after operation) 24 hour

Health (Anon 2003), and the National Audit Office report in 2004 (Anon 2004). In 2005 the Scottish NHS published recommendations for good antimicrobial practice in acute hospitals, which included clear lines of accountability to the Chief Executive and recommendations for internal structures and monitoring (Antimicrobial prescribing policy and practice in Scotland: recommendations for good antimicrobial practice in acute hospitals. NHS Scottish Executive publications 2005 at http://www.scotland.gov.uk/Publications/2005/09/02132609/26114).

At the end of 2003 the Department of Health in England announced that acute Trusts must appoint a Director of Infection Prevention and Control (DIPC), who must report directly to the Chief Executive and be a Board member (Anon 2003). The DIPC has the authority to manage and challenge all antibiotic practice. This bold initiative was to ensure Trusts understood the corporate responsibility and public health leadership that must be provided to tackle infection prevention and control which includes antibiotic management. However, how this initiative is actually being adopted and implemented in England needs some further study. Some experts do not have the leadership background, or strategic skills. Some Trusts have put the Director of Nursing in this role, which may be appropriate in some Trusts if this director is an influential leader, and has the relevant support and strong working relationships. However, this may undermine the medical credibility and influence of the DIPC post with senior consultants and their clinical peers.

The hospital board needs to have an understanding of the goals of antibiotic management beyond expenditure. The board must foster awareness in senior managers and senior clinicians on the significance and importance of managing antibiotics, and the shared accountability for delivery of an effective program. Experts in antibiotic use will be required to think more strategically and work more effectively with managers to embed antibiotic prescribing in the performance goals for the Trust.

Addressing change, strategy and policy across an organization from within the microbiology laboratory is impossible. Experts in infection and antibiotics must be given more time, and encouraged to develop new skills and engage with experts who possess these organizational and management skills, to work toward a shared goal (Edwards et al. 2002). A systems-based approach is required, integrating and embedding goals in antibiotic management with the other goals in the hospital's overall strategy, annual plans, and directorate objectives. This should lead to an organizational reinforcement of best practice, and a cultural and behavioral change across the whole organization (Holmes 2006).

## *Systems of Monitoring and Feedback*

A framework for monitoring, providing feedback, and improvement is essential to develop organizational learning and reinforce behavior. An appreciation of the different terms used regarding measurements of delivery of clinical care is important. While clinicians understand the value and significance of surveillance and clinical audit, the term "performance management" is one more widely used and understood by hospital managers. Much can be learned from other industries and the business world. The balanced scorecard is now widely used in the NHS.

It was described by Kaplan and Norton (1996) as a framework to measure performance beyond finances in private industry, and to align performance measures with strategic missions and goals (so not only measuring performance but factors driving performance). It provides a good basis for executing strategy and managing change successfully, with the caution that "you only get what you measure"; that it can skew activity, and regular refreshing and updating are required. In 1998 the Department of Health published "First Class Service" (HSC 1998/113) which described the need for a framework that supported high quality standards, not just efficiency. In 1999 the NHS performance assessment framework was introduced, based on a balanced scorecard approach. This has since been taken further and supported by the Health Care Commission using key target and performance indicators for annual performance rating of Trusts. Caution must be exerted here, as much depends on the measures chosen, and it is significantly limited by the data quality and availability in NHS Trusts.

At a local level, many Trusts use balanced scorecards internally to oversee the management of each directorate. Many complex performance measures are distilled and summarized using a traffic light monitoring and warning system of red, amber, and green. This existing monitoring framework provides a useful tool to address antibiotic prescribing, as long as the Trust can provide regular, reliable surveillance and audit data on antibiotic prescribing. At one West London Trust (Holmes 2006) these directorate-based balanced scorecards have been used to integrate the performance monitoring of directorate-based antibiotic prescribing, alongside the monitoring of other infection-related performance measures and measures of performance in other areas, such as finance and human resources. In this Trust this framework is used as a means of reinforcing directorate accountability, the importance of antibiotic stewardship, and the integration of infection control with antibiotic control. Review of directorate-based data is a standing agenda item at the Trust Clinical Governance Committees. The data, and the fact that they are used, are collected using serial point prevalence studies on antibiotic prescriptions (Dean et al. 2002). These studies are organized and analyzed by pharmacists (a method widely adopted across U.K. hospitals) and represent an opportunity to highlight the pharmacist role in clinical management (The Audit Commission—A Spoonful of Sugar—Medicines Management in NHS Hospitals 18 Dec 2001).

The implementation and monitoring of the delivery of the antibiotic care bundle (as described above) could also provide a quality indicator of antibiotic stewardship for an individual hospital, and internally provide a useful monitoring tool for the clinical directorates.

## *Maximizing the Role of Pharmacists*

The United Kingdom is at a great advantage of having clinical and ward based pharmacists. The role of the pharmacist is not new, and has been accepted as a valuable and expert member of the multidisciplinary infection team in many Trusts, but is not yet universal (Knox et al. 2003, Knox and Holmes 2004).

The senior role of pharmacists in clinical management is not as developed as in the United States. However, this is changing, and a new breed of senior specialist clinical pharmacists is being created in the United Kingdom. This is aided by sustained professional development and postgraduate expertise, such as that provided by a dedicated MSc program for pharmacists collaboratively run by the Health Protection Agency, Imperial College, and Hammersmith Hospitals NHS Trust (http://www1.imperial.ac.uk/medicine/about/divisions/is/idm/training/mscpharmacist) These pharmacists also have a U.K.-wide professional network supporting their position (http://www.ukcpa.org/pharmacist/infectionmanagement/). Their role was being promoted in the United Kingdom by the provision of additional funding for 3 years by the Department of Health, to enhance clinical pharmacy activity in prudent use of antibiotics in hospitals [Chief Pharmaceutical Officer letter: PL CPHO (2003)3. Hospital Pharmacy initiative for promoting prudent use of antibiotics in hospitals 09/06/2003]. Specialists in infection and senior managers are recognizing the importance of this expertise in contributing to the overall quality of medicines management for anti-infectives, and the delivery of antibiotic stewardship in hospitals. Furthermore, the role and expertise of pharmacists, particularly in education and training, will become even more valuable with the increasing turnover of junior medical staff.

## *Understanding the Blocks*

Blocks in the implementation of best practice need to be understood. Most hospitals are keenly aware of blocks related to logistics, poor Information Technology systems, long laboratory turnaround times and resistance reporting, poor communications, and even poorer documentation. However, organizations may be less familiar with the significant cultural and behavioral blocks to optimizing antibiotic prescribing. Understanding the cultural context and behavior is a key component of any change management strategy. It is one that has not been addressed adequately by those wishing to influence policy, although it is well recognized by commercial companies. Through this comes an understanding of the barriers to implementation, beyond those related to logistics. This was well described in a recent paper from Canada exploring the barriers to delivering surgical antibiotic prophylaxis appropriately (Tan et al. 2006). Although the timing of the dose of prophylactic antibiotics prior to surgery is critical to ensure its effectiveness to prevent surgical infection (Classen et al. 1992), the simple delivery of this first dose at the right time is a challenge that many institutes cannot address. It is only through examining the barriers to this process that success can be achieved. The authors demonstrate that these barriers are not just the existing systems and logistics, but also the significant cultural and behavioral aspects, and the professional and social context. They state that “this is an example of the well described difficulty of transferring evidence based guidelines into practice.” They identified that in addition to clear blocks presented by work flow, provision of intravenous access, communication, and documentation, there were two important areas outside logistics that represented significant blocks: perceptions of priorities and

roles. Surgeons and anesthetists classed giving antibiotics as low priority among their main responsibilities, and had no agreement on whose role or responsibility it was to oversee the administration of antibiotic prophylaxis. Without addressing these two fundamental issues an improvement in the delivery of antibiotic prophylaxis for surgery is unlikely to be achieved

### *Incentives for Clinicians*

Incentives are important to reinforce good practice and awareness, particularly when education and training regarding antibiotic use and infection prevention and control may be inadequate in undergraduate and then in postgraduate specialist clinical training. A greater appreciation of how the prudent use of antibiotics will improve the clinical outcome of their own patients is the most fundamental incentive. However, experts in antibiotics have not universally achieved this, and as discussed above they must explore the reasons why and modify their approach. Powerful clinical role models for clinicians-in-training play an important part in shaping behavior. Merit awards that recognize individuals as role models, leadership in improving antibiotic prescribing, actions taken to improve local practice and awareness would be useful incentives. Peer recognition is key, and validation by peers and merit award committees would be a strong positive reinforcement.

Appraisals for consultants should address their role and activities in preventing hospital acquired infection (http://www.bma.org.uk/ap.nsf/Attachments-ByTitle/PDFHealthcareAssocInfect/$FILE/HCAIs.pdf). The appraisal should also address antibiotic prescribing habits and the individual's role as leading on best practice, and delivering on education, audit, and quality assurance. It may also be possible to link the annual appraisal to performance-related pay. A means developed locally in West London (Holmes 2006) to encourage surgeons not to continue with prolonged unnecessary prophylaxis postoperatively is to classify surgical cases as Hospital-Acquired Infections, when antibiotics are administered longer than 24 hours postoperatively. As prescribing improves, it may be possible to consider significant breaches from best practice as clinical incidents that should be reported, investigated, and learned from. Patient choice will also provide an incentive to hospitals and individual consultants if performance regarding the quality of antibiotic prescribing is made public, provided it is presented in a suitable and sensible format.

## Conclusion

The widespread use of rapid DNA-based tests to identify common organisms and their resistance patterns would revolutionize the practice of infection management, and theoretically have a massive impact on the control of antibiotic resistance. However, in the absence of new molecular diagnostic tests, much can be done to enhance existing antibiotic prescribing practice, through initiatives

that address prescribing behavior at the individual level and in the context of the whole organization. Parallel development and research into better systems to optimize antibiotic prescribing in hospitals is critical to fully realize the potential of bringing molecular tests into clinical practice. Only then can we succeed in influencing and improving antibiotic use and advancing the care of today's patients and our future patients.

## *References*

Agranoff, D., A. Stich, et al. (2005) Proteomic fingerprinting for the diagnosis of human African trypanosomiasis. *Trends Parasitol* 21(4):154–7.

Anon (2003) Winning Ways: Working together to reduce healthcare associated infection in England. Report of the Chief Medical Officer, Department of Health.

Anon (2004) Improving patient care by reducing the risk of hospital acquired infection: A progress report. U.K. National Audit Office.

Belanger, S. D., M. Boissinot, et al. (2003) Rapid detection of Clostridium difficile in feces by real-time PCR. *J Clin Microbiol* 41(2):730–4.

Bergeron M.G. and M.Ouellette(1998) Minireview, Preventing Antibiotic Resistance through Rapid Genotypic Identification of Bacteria and of Their Antibiotic Resistance Genes in the Clinical Microbiology Laboratory. *J chin Micro* 36(8):2169-72.

Boissinot, M. and M. G. Bergeron (2002) Toward rapid real-time molecular diagnostic to guide smart use of antimicrobials. *Curr Opin Microbiol* 5(5):478–82.

Bryant, P. A., D. Venter, et al. (2004) Chips with everything: DNA microarrays in infectious diseases. *Lancet Infect Dis* 4(2):100–11.

Call, D. R., M. K. Bakko, et al. (2003) Identifying antimicrobial resistance genes with DNA microarrays. *Antimicrob Agents Chemother* 47(10):3290–5.

Classen, D. C., R. S. Evans, et al. (1992) The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 326(5):281–6.

Cooker, F. J., A.H. Holmes (2007) The missing care bundle: antibiotic prescribing in hospitals, *Int J Antimicrob Agents* doi: 10.1016/j.ijantimicag.2007.03.003.

Cooper, B. S., S. P. Stone, et al. (2003) Systematic review of isolation policies in the hospital management of methicillin-resistant Staphylococcus aureus: A review of the literature with epidemiological and economic modelling. *Health Technol Assess* 7(39):1–194.

Corona, A., G. Bertolini, et al. (2003) Variability of treatment duration for bacteraemia in the critically ill: A multinational survey. *J Antimicrob Chemother* 52(5):849–52.

Coyne, S. R., P. D. Craw, et al. (2004) Comparative analysis of the Schleicher and Schuell IsoCode Stix DNA isolation device and the Qiagen QIAamp DNA Mini Kit. *J Clin Microbiol* 42(10):4859–62.

Davey, P., E. Brown, et al. (2006) Systematic review of antimicrobial drug prescribing in hospitals. *Emerg Infect Dis* 12(2):211–6.

Dean, B., W. Lawson, et al. (2002) The use of serial point prevalence studies to investigate antiinfective prescribing. *Int J Pharm Pract* 10: 121–5.

Diep, B. A., S. R. Gill, et al. (2006) Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant Staphylococcus aureus. *Lancet* 367:731–9.

Edwards, N., M. J. Kornacki, et al. (2002) Unhappy doctors: What are the causes and what can be done? BMJ 324:835–8.

Espy, M. J., J. R. Uhl, et al. (2006) Real-time PCR in clinical microbiology: Applications for routine laboratory testing. *Clin Microbiol Rev* 19:165–256.

Evans, R. S., S. L. Pestotnik, et al. (1998) A computer-assisted management program for antibiotics and other antiinfective agents. *N Engl J Med* 338:232–8.

Fleischmann, R. D., M. D. Adams, et al. (1995) Whole-genome random sequencing and assembly of Haemophilus influenzae Rd. *Science* 269:496–512.

Foster, K. R. and H. Grundmann (2006) Do we need to put society first? The potential for tragedy in antimicrobial resistance. *PLoS Med* 3(2): e29.

Goldmann, D. A., R. A. Weinstein, et al. (1996) Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. JAMA 275: 234–40.

Hackett, S. J., M. Guiver, et al. (2002) Meningococcal bacterial DNA load at presentation correlates with disease severity. *Arch Dis Child* 86: 44–6.

Hardy, K. J., B. A. Oppenheim, et al. (2006) Use of variations in staphylococcal interspersed repeat units for molecular typing of methicillin-resistant Staphylococcus aureus strains. *J Clin Microbiol* 44: 271–3.

Holland, C. A. and F. L. Kiechle (2005) Point-of-care molecular diagnostic systems—Past, present and future. *Curr Opin Microbiol* 8: 504–9.

Holmes, A. (2006) Organisational change for infection protection. Developing an organisational model for infection control at Hammersmith Hospitals trust. *Health Service Journal* 8: 19–22,
http://www.publicservice.co.uk/pdf/health/issue8/H8%20Dr%20Alison%20Holmes%20ATL.pdf

Huletsky, A., R. Giroux, et al. (2004) New real-time PCR assay for rapid detection of methicillin-resistant Staphylococcus aureus directly from specimens containing a mixture of staphylococci. *J Clin Microbiol* 42: 1875–84.

Huletsky, A., P. Lebel, et al. (2005) Identification of methicillin-resistant Staphylococcus aureus carriage in less than 1 hour during a hospital surveillance program. *Clin Infect Dis* 40: 976–81.

Kaplan, R. D.P. Norton (1996) *The Balanced Scorecard: Translating Strategy into Action*. Harvard Business School Press.

Knox, K., W. Lawson, et al. (2003) Multidisciplinary antimicrobial management and the role of the infectious diseases pharmacist—A UK perspective. *J Hosp Infect* 53: 85–90.

Knox, K. L., Lawson, A. Holmes (2004) *Multidisciplinary Antimicrobial Management Teams and the Role of the Pharmacist in Management of Infection*.

Kuroda, M., T. Ohta, et al. (2001) Whole genome sequencing of meticillin-resistant Staphylococcus aureus. *Lancet* 357: 1225–40.

Kusunoki, S., T. Ezaki, et al. (1991) Application of colorimetric microdilution plate hybridization for rapid genetic identification of 22 Mycobacterium species. *J Clin Microbiol* 29: 1596–603.

Lambert, H. P. (1999) Don't keep taking the tablets? *Lancet* 354: 943–5.

Lapierre, P., A. Huletsky, et al. (2003) Real-time PCR assay for detection of fluoroquinolone resistance associated with grlA mutations in Staphylococcus aureus. *J Clin Microbiol* 41: 3246–51.

Maiden, M. C., J. A. Bygraves, et al. (1998) Multilocus sequence typing: A portable approach to the identification of clones within populations of pathogenic microorganisms. *Proc Natl Acad Sci USA* 95: 3140–5.

Morozumi, M., E. Nakayama, et al. (2006) Simultaneous detection of pathogens in clinical samples from patients with community-acquired pneumonia by real-time PCR with pathogen-specific molecular beacon probes. *J Clin Microbiol* 44: 1440–6.

Mortimer, P. and C. Arnold (2001) FAFLP: last word in microbial genotyping? *J Med Microbiol* 50: 393–5.

Nikkari, S., I. J. McLaughlin, et al. (2001) Does blood of healthy subjects contain bacterial ribosomal DNA? *J Clin Microbiol* 39: 1956–9.

Peters, R. P., T. Mohammadi, et al. (2004a) Detection of bacterial DNA in blood samples from febrile patients: Underestimated infection or emerging contamination? *FEMS Immunol Med Microbiol* 42: 249–53.

Peters, R. P., M. A. van Agtmael, et al. (2004b) New developments in the diagnosis of bloodstream infections. *Lancet Infect Dis* 4: 751–60.

Peters, R. P., P. H. Savelkoul, et al. (2006) Faster identification of pathogens in positive blood cultures by fluorescence in situ hybridization in routine practice. *J Clin Microbiol* 44: 119–23.

Picard, F. J. and M. G. Bergeron (2002) Rapid molecular theranostics in infectious diseases. *Drug Discov Today* 7: 1092–101.

Pulcini, C., C. Pradier, et al. (2006) Factors associated with adherence to infectious diseases advice in two intensive care units. *J Antimicrob Chemother* 57: 546–50.

Relman, D. A. (2003) Shedding light on microbial detection. *N Engl J Med* 349: 2162–3.

Rider, T. H., M. S. Petrovick, et al. (2003) A B cell-based sensor for rapid identification of pathogens. *Science* 301: 213–5.

Roger, M., P. St-Antoine, et al. (2001) Vancomycin-resistant enterococci in health care facilities. *N Engl J Med* 345: 768–9.

Seaton, R. A., D. Nathwani, et al. (1999) Clinical record keeping in patients receiving antibiotics in hospital. *Health Bull (Edinb)* 57: 128–33.

Silversin, J. and M.J. kornacki (2000) *Leading Physicians through Change: How to Achieve and Sustain Results*. American College of Physician Executives.

Sintchenko, V., J. R. Iredell, et al. (2005) Handheld computer-based decision support reduces patient length of stay and antibiotic prescribing in critical care. *J Am Med Inform Assoc* 12: 398–402.

Stefanelli, P., A. Carattoli, et al. (2003) Prediction of decreased susceptibility to penicillin of Neisseria meningitidis strains by real-time PCR. *J Clin Microbiol* 41: 4666–70.

Tan, J. A., V. N. Naik, et al. (2006) Exploring obstacles to proper timing of prophylactic antibiotics for surgical site infections. *Qual Saf Health Care* 15: 32–8.

Uhl, J. R., S. C. Adamson, et al. (2003) Comparison of LightCycler PCR, rapid antigen immunoassay, and culture for detection of group A streptococci from throat swabs. *J Clin Microbiol* 41: 242–9.

Uhl, J. R., E. A. Vetter, et al. (2005) Use of the Roche LightCycler Strep B assay for detection of group B streptococcus from vaginal and rectal swabs. *J Clin Microbiol* 43: 4046–51.

Wolk, D., S. Mitchell, et al. (2001) Principles of molecular microbiology testing methods. *Infect Dis Clin North Am* 15: 1157–204.

Yang, S. and R. E. Rothman (2004) PCR-based diagnostics for infectious diseases: Uses, limitations, and future applications in acute-care settings. *Lancet Infect Dis* 4: 337–48.

# Chapter 8
# Antimicrobial Resistance: Preventable or Inevitable?
## Problem of the Era from Two Perspectives

Duygu Yazgan Aksoy*, Mine Durusu Tanriover*, and Serhat Unal**

## Introduction

An antimicrobial agent is anything that inhibits microbial growth; unfortunately, introduction of a new antimicrobial agent is usually followed by the rapid emergence of resistance. Resistance can be intrinsic, which implies that not all species are intrinsically susceptible to all antimicrobials, or acquired depending on genetic or biochemical mechanisms used by the microorganism. Genetic resistance can be temporary that can change according to the growth conditions or permanent due to the mutation or acquisition of extrinsic DNA from outside source. Production of drug-inactivating enzymes, modification of an existing target, acquisition of a target bypass system, reduced cell permeability, and drug removal from the cell are the five mechanisms which microorganisms use to acquire resistance through biochemical basis.[1]

Many factors contribute to high rates of resistance; misuse of antibiotics by health professionals, unskilled practitioners, and laypersons as well as by the public (where antibiotics can be purchased without prescription), poor drug quality, unhygienic conditions accounting for the spread of resistant bacteria, and inadequate surveillance (lack of information from routine antimicrobial susceptibility testing of bacterial isolates and surveillance testing of bacterial isolates and of antibiotic resistance).[2,3] All of the mentioned factors are key points for good clinical practice and for rational policies against antibiotic resistance.

As concerns about antimicrobial resistance increase, efforts of the pharmaceutical industry to develop new drugs increase because of the possibility of running out of effective antimicrobial agents. Resistance to antimicrobials is not a new phenomenon. Shortly after the introduction of penicillin in the 1940s, the proportion of penicillin-resistant strains had risen to 14%, which is over 90% for *Staphylococcus aureus* today.[4] Formerly, resistant organisms were considered to be a problem of hospitals, but today resistance problems exist and have increased in the community in a parallel manner to the hospitals. The resistance problem in the community may even become more serious since many physicians are unaware of

the scope and frequency of the resistance. In this review, major aspects of antimicrobial resistance in hospitals and in the community are summarized.

## Antimicrobial Resistance in the Community and Hospitals

Urinary tract infections (UTI), respiratory tract infections (RTI), and tuberculosis are increasingly receiving attention from the view point of antimicrobial resistance, both in the community and hospital setting.

The resistance problem is particularly serious in the hospital environment, where the selection pressure caused by massive antimicrobial use, combined with epidemic spread of selected strains, is responsible for the emergence of multidrug-resistant (MDR) microorganisms such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus* species (VRE), *Pseudomonas aeruginosa*, and *Acinebacter baumannii*.[5–9] According to the Centers for Disease Control and Prevention (CDC), more than 70% of bacteria now causing hospital acquired infections are resistant to at least one of the drugs that are most commonly used to treat them.[10] Especially the intensive care units (ICUs) contribute to nosocomial infections through catheter-related bloodstream infections, ventilator-associated pneumonias (VAP), and surgical site infections. Prevention of development of MDR pathogens should be the main goal of antimicrobial policy of ICUs, and adherence to preventive measures by ICU staff is thus crucial for a successful risk reduction strategy.[11] From this point of view ICUs should receive more attention from hospital epidemiology and infection control units.[12]

### *Urinary Tract Infections*

UTI is an important problem with regard to its frequency. Of women between 20 and 40 years of age, 25 to 35% have had at least one episode of UTI.[13] UTIs are most often caused by Gram-negative bacilli; approximately 80% of uncomplicated UTIs are caused by *Escherichia coli*, and the rest with others such as enterococci, *Staphylococcus saprophyticus, Klebsiella* spp., and *Proteus mirabilis*.[14] Unfortunately, many strains of *E. coli* have become resistant to ampicillin because of expression of β-lactamases and this has resulted in increased use of co-trimoxazole (trimethoprim–sulfamethoxazole) over the last decade.[15] Since the publication of guidelines for the treatment of uncomplicated UTIs and pyelonephritis by the Infectious Diseases Society of America (IDSA) in 1999, the dramatic change in the pattern of resistance of uropathogens warrants reevaluation of guidelines.[16] The most recent IDSA guideline recommends co-trimoxazole, double strength, 1 tablet twice daily orally for 3 days, as the treatment of choice for uncomplicated UTIs.[16] Although co-trimoxazole has been recommended as first line treatment for women with uncomplicated UTIs, its clinical utility has dramatically decreased by the emergence of resistance. Recent surveillance studies indicate that 18–25% of bacterial pathogens isolated from patients with UTIs in the United States and Canada are resistant to co-trimoxazole and these rates are even higher (up to 45%) in Europe and

Latin America.[15] Factors associated with co-trimoxazole resistance are recent antibiotic exposures, recent hospitalization, diabetes mellitus, three or more UTIs in the past year, and possibly use of oral contraceptives or estrogen-replacement drugs.[17] IDSA recommends that empirical treatment of UTIs should be switched from co-trimoxazole to another agent in the event of high resistance in the community; in that case, the fluoroquinolones have the greatest efficacy.[16] As stated by Miller and Tang, this recommendation has two major limitations.[18] First, the rationale for the 10 to 20% cutoff is not well delineated. This cutoff is most probably chosen on the basis of clinical cure percentages and cost-effectiveness studies, since treatment costs become unacceptably high when co-trimoxazole resistance exceeds the 10 to 20% threshold.[18] Le and Miller found that fluoroquinolones become less expensive when co-trimoxazole resistance exceeds 22% in the community, which has been supported by a subsequent cost analysis.[19,20] In 2004, the *Sanford Guide to Antimicrobial Therapy* stated that co-trimoxazole is recommended in areas where local resistance is lower than 20%, but if it exceeds 20%, fluoroquinolones should be given.[21] The problem with this statement, which is also the second limitation of IDSA guidelines, is that the empirical use of fluoroquinolones may contribute to the emergence of fluoroquinolone-resistant bacteria.[16,18] Until 1999, fluoroquinolone-resistant isolates were not observed in patients with uncomplicated UTIs, but in 2001, fluoroquinolone-resistant *E. coli* emerged and accounted for about 8% of all *E. coli* isolates. Fluoroquinolone resistance rates of *E. coli* were reported between 8 and 35% in different series.[22–24] Strong and significant relationship between consumption of ciprofloxacin and resistance to it has been documented.[25] Every attempt should be made to decrease unnecessary antimicrobial use such as levofloxacin and ciprofloxacin and follow local antibacterial resistance data to guide empirical antibiotic therapy better.[26–32] With this information and available data on local antibiotic resistance patterns, clinicians must judge whether co-trimoxazole or an alternative antibiotic should be used empirically, when co-trimoxazole resistance exceeds 10 to 20% in the community.

Emergence of resistance has been more marked in hospitals than in general practice with regard to UTIs.[33] Hospital-acquired UTIs account for at least 40% of all nosocomial infections and are mainly associated with catheters.[34–36] Nosocomial bacteriuria develops in up to 25% of patients who have a urinary catheter for 7 days or more, with a daily cumulative risk of 5%. Moreover, the pathogens involved are fully exposed to the hospital environment, including antibiotic pressure, foreign bodies, or altered growth conditions. As a result, hospital-acquired UTIs comprise perhaps the largest institutional reservoir of nosocomial antibiotic-resistant pathogens.[36] Although *E. coli* is also the most frequently isolated bacterium in the nosocomial setting, the etiology of hospital-acquired UTIs is heterogeneous and covers a wide range of Gram-negative and Gram-positive species. Perrin et al. reported that nosocomial strains of *E. coli* isolated from UTIs are more resistant to amoxicillin, first generation quinolones, and co-trimoxazole.[37] The resistance pattern of microorganisms causing nosocomial UTIs was reported to be similar in both North America and Europe based on the studies SENTRY and ESGNI-003.[38,39] *E. coli* strains

showed the highest resistance to ampicillin (42%) and co-trimoxazole (23%), while being very susceptible to fluoroquinolones, nitrofurantoin, imipenem, and aminoglycosides. *Klebsiella* spp. demonstrated very high susceptibility profiles for third- and fourth-generation cephalosporins (>95%), imipenem (100%), piperacillin/tazobactam (95%), aminoglycosides (>95%), and fluoroquinolones (>92%).[38] The European Study Group on Nosocomial Infections also evaluated antimicrobial susceptibility against hospital-acquired urinary isolates in 29 countries. In this study non-European Union countries tended to have higher rates of *E. coli* resistance than European Union countries.[39] Another study from Europe revealed the highest resistance rate for ampicillin (51%), followed by cefazolin (44%) and co-trimoxazole (45%).[40] Several strategies have been developed to slow antibiotic resistance: lowering antibiotic consumption (not treating asymptomatic bacteriuria except under special conditions), antibiotic cycling (being careful not to overuse one group of antibiotics and using tailored empiric therapy of UTIs), and new dosing strategies for antibiotics (dosing should be chosen in order to surpass the upper boundary so-called "mutant selection window").[41]

Organisms producing extended-spectrum β-lactamases (ESBLs) have emerged as problematic microorganisms in hospitals. The frequency, although still low, showed an upward trend compared to the last decade.[42–44] As ESBLs exhibit resistance to a wide variety of antimicrobial agents, carbapenems represent the only class of antibiotics uniformly active against ESBLs.[45,46] Old age, male gender, presence of an instrumentation (urinary catheter, central venous catheter, gastrostomy tube, etc.), duration of hospitalization before infection, higher APACHE II score, and level of function (confinement to bed with debilitation) are all documented risk factors, though prior use of antibiotics with longer duration seems to be an independent risk factor.[44,47–52] Mortality rates increase dramatically if the patients are not treated on time with appropriate antibiotics.[48] In spite of the belief that ESBLs are a problem of hospitals, Einhorn et al. reported that in 14% of patients harboring ESBLs, infections were community acquired.[51–53] They emphasized the risk in ambulatory patients who have chronic conditions; in fact, the risk factors described for inpatients also increase the possibility of harboring ESBLs out of the hospitals.

## *Respiratory Tract Infections*

Two to three million cases of community-acquired pneumonia (CAP) are reported in the United States each year, resulting in approximately 10 million physician visits.[54] In cases in which an etiologic agent is documented, *Streptococcus pneumoniae* is the leading cause. Attributable mortality and morbidity have remained essentially unchanged in recent decades, despite the emergence of new antimicrobial options and improvement in critical care medicine.[54,55] Antimicrobial resistance results in high hospitalization rates, mortality, and costs.[56] A large retrospective study concluded that infections caused by penicillin-resistant *S. pneumoniae* with penicillin minimum inhibitory concentration

(MIC) ≥ 4 μg/ml or cefotaxime MIC ≥ 2 μg/ml were associated with increased mortality in the multivariate model, but only after excluding short-term mortality (within 4 days), especially in bacteremic patients.[57] Age less than 6 years and greater than 70 years, recent antimicrobial therapy, immunosuppression, HIV, presence of underlying disease, recent or current hospitalization, and institutionalization were some of the risk factors associated with resistant *S. pneumoniae*.[58] As drug-resistant strains have increased, penicillin resistant *S. pneumoniae* isolates have reached 25–35% in the United States and have surpassed 40% in some areas of Europe.[59–61] When penicillin resistance is identified, resistance to other antibiotics, like cephalosporins, macrolides, doxycycline, and co-trimoxazole, is generally anticipated.[62] According to the 2002–2003 Tracking Resistance in the US Today (TRUST) 7 study, *S. pneumoniae* susceptibility was 96.1% for ceftriaxone, 93.4% for amoxicillin–clavulanate, 72.2% for azithromycin, and 99.1% for levofloxacin.[63] In the TRUST 8 data, susceptibility rates were similar. In these two studies, it has been documented that resistance varies among geographic regions of the United States. In association with an increase in macrolide use from 1993 to 1999, macrolide resistance in *S. pneumoniae* rose up to 20.4% by the year 2002.[64] Doern et al. reported a resistance rate around 30% for macrolides recently; in the same study 22.3% of *S. pneumoniae* was MDR.[65]

Other causative microorganisms of CAP are *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pyogenes, Moraxella catarrhalis, Klebsiella pneumoniae, Legionella* spp., viruses, and other Gram-negative rods.[54] In patients hospitalized due to CAP, *P. aeruginosa* has also been recovered.[55] *H. influenzae* and *M. catarrhalis* were shown to be significantly resistant to first-generation cephalosporins and other β-lactams.[63] Abdel-Rahman et al. reported ampicillin resistance in 20% and multidrug resistance in 5.4% of all isolates of *H. influenzae* in Saudi Arabia, where antibiotics are commonly sold over the counter.[66] Being aware of the resistance rates observed in *H. influenzae*, clinicians should choose an antibiotic other than ampicillin, when empirical antibiotic therapy is needed.

Fluoroquinolone resistance of *S. pneumoniae* has not yet become a significant clinical and epidemiological problem, presenting an overall 1% resistance.[63,67,68] However, the resistance of *S. pneumoniae* to ciprofloxacin doubled from 1999 to 2001 (from 1.2% to 2.7%) as well as to levofloxacin (from 0.6% to 1.3%).[69] Recently, Bhavnani et al. reported a 50% increase in levofloxacin MIC values for *S. pneumoniae* from 1997 to 2001 and this increase was closely associated with the increase in levofloxacin use, which increased from 0.4 to 4 prescriptions per 100 people over 6 years.[70]

Acute exacerbation of chronic bronchitis is mainly due to *H. influenzae* and *S. pneumoniae*, but not atypical microorganisms. In severe cases, Gram-negative microorganisms may be involved such as Enterobacteriaceae and *Pseudomonas*. Severe exacerbations of chronic obstructive pulmonary disease generally require hospitalization. In addition, patients with significant compromise of lung function may develop respiratory failure as a consequence of an acute exacerbation, and up

to 60% of these patients will require mechanical ventilation.[71] In this group of patients, the bacterial etiology correlates closely with the severity of the accompanying lung disease.[72] *S. pneumoniae* is the most common microorganism in patients with mild disease; *H. influenzae, M. catarrhalis*, Enterobacteriaceae, and *Pseudomonas* species are becoming more commonly encountered as disease severity increases.[71,72] The major resistance for *M. catarrhalis* is caused by β-lactamases, and this is also the case for *H. influenzae*. Among both, penicillin-resistant strains have increased through the last two decades.[58] Gatifloxacin, levofloxacin, and ciprofloxacin are active against all *M. catarrhalis* and *H. influenzae* isolates, and gatifloxacin and levofloxacin are active against $>$ 99% of *S. pneumoniae*. Amoxicillin–clavulanate, cefuroxime axetil, tetracycline, and fluoroquinolones (namely, levofloxacin and ciprofloxacin) remain effective against both *P. aeruginosa* and *Enterobacter cloacae;* these agents are also more active against common pathogens than macrolides.[73,74]

Hospital-acquired pneumonia (HAP), VAP, and healthcare-associated pneumonia (HCAP) constitute the rest of the RTIs treated in the hospitals. About 300,000 cases of HAP occur annually, and HAP has an attributable mortality rate of approximately 33 to 50%.[75] Compared to patients with CAP, patients with HAP are at greater risk for colonization and infection with a wider variety of MDR pathogens.[76] The major clinical strategies for HAP, VAP, and HCAP include initial management of the disease on the basis of time of onset and risk for MDR pathogens, adequate dosing during empirical therapy for MDR pathogens, and broad-spectrum initial antibiotic therapy followed by appropriate antibiotic deescalation to limit development of resistance.[76] Choosing the initial, appropriate antibiotic regimen is becoming much more difficult due to the rapid emergence of different types of MDR pathogens including *P. aeruginosa, K. pneumoniae, Acinetobacter* species, and MRSA. It is recommended that patients without MDR risk factors and early onset HAP or VAP initially be treated with ceftriaxone, ampicillin–sulbactam, ertapenem, or one of the fluoroquinolones (moxifloxacin, ciprofloxacin, or levofloxacin).[76] Considering the increased frequency of both penicillin resistance and MDR among *S. pneumoniae*, levofloxacin and moxifloxacin are preferred over ciprofloxacin. Patients with late-onset HAP, VAP, and HCAP or those with known risk factors for MDR pathogens should be treated with an antipseudomonal cephalosporin (cefepime or ceftazidime), a carbapenem (imipenem or meropenem), or piperacillin–tazobactam.[76] An antipseudomonal fluoroquinolone or an aminoglycoside might also be given. Linezolid or vancomycin should be added if there are risk factors for MRSA. *In vitro* resistance of the pathogen has been shown to correlate with clinical failure.[77] *K. pneumoniae*, which is an important pathogen involved in nosocomial infections, has been a growing problem. *K. pneumonia*e producing ESBL has become more prevalent, and is difficult to eradicate, since these organisms develop resistance to multiple antibiotics.

Nosocomial pneumonia therapy in ICU often requires excessive antibiotic use because of the associated high mortality rates.[63] An operational approach to reduce the amount and duration of antibiotic use in the ICU is to reevaluate the patients after initiation of therapy, using an operational criterion such as the

clinical pulmonary infection score (CPIS). Reevaluation with CPIS has been shown to successfully identify patients for whom short-course therapy would be appropriate.[74] This resulted in shorter durations and lower costs of antibiotic treatment and eventual decrease in antibiotic resistance.

## *Multidrug-Resistant Mycobacterium tuberculosis*

Infection by *Mycobacterium tuberculosis* remains a leading cause of death.[78] Along with unacceptably low cure rates and the continued spread of tuberculosis in the community, a major consequence of an inappropriate treatment is the selection of *M. tuberculosis* isolates that are resistant to antituberculosis drugs.[79] The widely used acronym MDR-TB (multidrug-resistant tuberculosis) indicates presence of *M. tuberculosis* resistance to at least isoniazid and rifampicin, which are the two fundemental components of any regimen for the treatment of drug-susceptible TB. MDR-TB emerged during the 1990s as a threat to TB control. While efforts to control MDR-TB were continuing, cases of TB that are resistant to all second-line drugs were reported, namely, extensively drug-resistant tuberculosis (XDR-TB).[80] CDC reports demonstrate that, during 2000–2004, of the 17,690 TB isolates studied, 20% were MDR and 2% were XDR. MDR-TB is more common in populations where compliance with the therapy is a problem and in those with HIV infection.[81] Improper treatment of resistant TB cases possibly led to the development of XDR-TB cases, even in countries like the United States where there are effective TB control programs.[80]

In drug-resistant TB cases, residual first-line drugs, such as ethambutol, pyrazinamide, and streptomycin, must be appropriately combined with additional second-line drugs, guided by individual susceptibility patterns. Of the second-line drugs, fluoroquinolones represent the only substantial therapeutic advance in the last 20 years.[82] Moxifloxacin, and new classes of drugs such as nitroimidazopyrans (PA-824) and diarylquinolines (R-207910) are promising future therapies. The management of MDR-TB needs expertise; the process of selecting drugs should rely on prior treatment history, results of susceptibility tests, and evaluation of the patient's adherence.[83]

## *Methicillin-Resistant Staphylococcus aureus*

Overall, *S. aureus* is reported to be the most common cause of bacterial infections involving the bloodstream, lower respiratory tract (CAP and HAP), and skin/soft tissue.[84] It is reported to be the leading organism responsible for VAP in Europe.[85] VAP due to MRSA significantly extends ICU length of stay and increases hospital costs.[86] A wide array of virulence mechanisms, an ability to persist in different environments, and an extraordinary potential to develop antimicrobial resistance contribute to the success of this organism as a human pathogen.[87,88] Naturally occurring MRSA isolates were identified soon after methicillin was introduced. Since methicillin resistance in *S. aureus* was first reported in the early 1960s, the proportion of Gram-positive pathogens that are

resistant to antimicrobial agents continues to increase both in the hospital setting, particularly in the ICU, and in the community.[84] In 1991, MRSA accounted for 35% of isolates in the United States, but that incidence has increased and now many hospitals are reporting MRSA rates as high as 50 to 70%.[89,90] In 2000, more than 50% of *S. aureus* isolates causing infections in ICUs were resistant to MRSA.[89–91] Methicillin resistance rates are highest in the nations of southern Europe (e.g., Italy, Greece, Portugal, and Turkey).[92] Being a resident of large tertiary-care hospitals, acute care or nursing homes, and proximity to other patients with MRSA are well known risk factors for MRSA infections as well as burns, surgical wounds, dialysis, indwelling intravenous catheters, prolonged hospitalization, advanced age, immunocompromise, and prior antibiotic administration.[58,93] Two recent meta-analyses demonstrated that bacteremia caused by MRSA was associated with significant mortality rates (29 and 36%, respectively) compared to bacteremia caused by methicillin-susceptible *S. aureus*.[94,95] Vancomycin and teicoplanin were accepted as the last choice of therapy for MRSA; however, in 1997 Hiramatsu et al. described the first clinical *S. aureus* isolate with intermediate resistance to vancomycin (MIC, 8 μg/ml).[96] Since then, resistance to both of these antimicrobial agents among Gram-positive pathogens has been reported.[96,97] Increased use of vancomycin has led to selective pressure and subsequent appearance of vancomycin intermediate and vancomycin resistant MRSA.[98] Quinupristin–dalfopristin, linezolid, and daptomycin are alternative agents in glycopeptide-resistant cases.[99] Unfortunately, cases with quinopristin-dalfopristin and linezolid resistant *S. aureus* have also been reported.[84,100] Controlling overuse and misuse of antibiotics, but more importantly uniform infection-control practices to prevent transmission are specifically important to overcome the increase in methicillin resistance. The Netherlands was able to control the spread of MRSA with an aggressive strategy of vigilant surveillance and infection control measures.[101]

The issue that has been receiving increasing attention is the community-acquired MRSA in patients without risk factors. Patients with community-acquired MRSA, but without evidence of any risk factors suggest that MRSA is becoming a common organism in the community and may well become more prevalent than methicillin-susceptible *S. aureus* with time.[58,102] Community-acquired MRSA infections were reported in the United States as early as the 1980s, but many of these episodes were associated with typical risk factors for MRSA acquisition such as hospitalization and intravenous drug use.[103,104] In 1999, four cases of community-acquired MRSA were reported in the U.S. Midwest.[105] All four cases were pediatric patients, none of whom had predisposing risk factors, and all died. In each case there was a delay in receiving appropriate therapy. In 2005, CDC defined community-acquired MRSA infection as: identification of MRSA in a patient with signs and symptoms of infection either in the outpatient setting or within 48 hours after admission to a hospital, with no history of MRSA infection or colonization, no history of admission to a hospital or nursing home during the previous year, and absence of dialysis, surgery, permanent indwelling catheters, or medical devices that pass through the skin to the body.[106] The clinical features and outcomes are similar to those seen

with methicillin-susceptible strains including sepsis, endocarditis, and metastatic infection.[107] Recently, Hidron et al. reported HIV, hospitalization, antibiotic use within 3 months, and diagnosis of soft tissue and skin infection at admission as risk factors for colonization with MRSA in an urban hospital.[108] These risk factors, as well as indwelling urinary catheters and nursing home residence, were reported to be associated with the presence of bacteremia at hospital admission previously.[109] There is controversy whether the concept of "community-acquired MRSA" really reflects the MRSA acquired in the community. In fact, MRSA colonization may persist for months and occurs frequently among household and community contacts of patients with hospital-acquired MRSA. However, MRSA acquired in the community differs from healthcare-associated MRSA both phenotypically (non-MDR versus MDR) and genotypically (type IV SCCmec versus type III SCCmec).[107,110] The evolution of MRSA from hospital to community infection is reminiscent of the spread of penicillinase-producing *S. aureus* from hospitals to the community, but the relationship between community-acquired and hospital-acquired MRSA isolates is poorly understood. Frequent prescription of β-lactamase penicillins and cephalosporins in the community probably contributed to the selection of community-acquired MRSA strains.[111]

## *Pseudomonas aeruginosa*

*P. aeruginosa* is typically an opportunist that seldom causes disease in healthy subjects and is mostly a nosocomial pathogen. According to the data of the CDC National Nosocomial Infection Surveillance System, *P. aeruginosa* was the second most common cause of nosocomial pneumonia, third most common cause of urinary tract infections, and seventh most common cause of nosocomial bacteremia.[112] UTIs caused by *P. aeruginosa* are usually related to catheterization or other invasive procedures.[113,114] In Europe, *P. aeruginosa* was found to be the third most common isolate from nosocomial infections in ICUs.[115] It is among the leading causes of nosocomial pneumonia, especially in mechanically ventilated patients. Mortality rates ranging from 40% to more than 60% were reported in bacteremic nosocomial pneumonia and VAP.[116–118] *P. aeruginosa* bacteremia and septic shock are primarily observed in immunocompromised patients and are associated with high mortality rates (from one third to almost two-thirds of cases).[119–121] All situations associated with severe neutropenia and mucosal ulcerations, such as hematological malignancies, cancer chemotherapy, and organ transplantation, are risk factors; diabetes mellitus, immunoglobulin deficiency states, severe burns, steroid therapy, surgery, and the use of invasive devices also predispose to *P. aeruginosa* bacteremia.[122–126] In a recent surveillance study on nosocomial bloodstream isolates, *P. aeruginosa* was the third most common pathogen.[46]

*P. aeruginosa* is intrinsically resistant to many antimicrobial agents, including most β-lactams, the older quinolones, chloramphenicol, tetracycline, macrolides, co-trimoxazole, and rifampin. The most important antipseudomonal agents include some β-lactams (ticarcillin, ureidopenicillins, piperacillin, cefoperazone,

ceftazidime, cefepime, aztreonam, imipenem, and meropenem), aminoglycosides (gentamicin, tobramycin, netilmicin, and amikacin), and fluoroquinolones (of which ciprofloxacin remains the most active compound).[127,128] Polymyxins are also active, but due to their higher toxicity, they are usually considered only for MDR strains.[129] Surveillance of *P. aeruginosa* susceptibility is particularly important because of the large number of cases in which antimicrobial chemotherapy must be initiated empirically, and the higher failure rates when the pathogen proves to be resistant to the agents prescribed empirically.[130] Recent data emphasize that amikacin, piperacillin–tazobactam, and carbapenems remain the most active drugs worldwide, while ticarcillin and aztreonam show the lowest activities.[131] Susceptibility rates indicate significant geographical differences; overall, the highest rates are observed in North America and the Asian Pacific region, while the lowest rates are observed in Latin America, with Europe being in an intermediate position. Especially in ICUs, where *P. aeruginosa* is one of the leading causes of severe nosocomial infections, susceptibility rates are lower than in general wards for some β-lactams (carbapenems, ceftazidime, ticarcillin–clavulanate) and, in Europe, also for ciprofloxacin and gentamicin, while remarkable differences are not observed with other drugs, such as piperacillin–tazobactam, cefepime, and amikacin.[132,133] Overall, higher resistance rates in ICUs were observed in Europe compared to the United States; there is also a great diversity of resistance rates for different drugs in different European settings at different times.[134]

The increasing trend of resistance is especially important for the fluoroquinolones, for which resistance seems to increase faster than for other antimicrobial agents in the United States, Europe, and Latin America. For aminoglycosides and β-lactams, increase in resistance is more prominent in Europe.[132,135–137] In the SENTRY surveillance program, the rates of MDR (defined as being resistant to piperacillin, ceftazidime, imipenem, and gentamicin) were found to reflect geographical differences, being higher in Latin America, lower in Europe, and even lower in North America and the Asia-Pacific region.[137] MDR strains are higher in ICUs since they tend to cause outbreaks. Overall, there has been an increase in rates from 13% in 1997 to 21% in 2001.[138] The appearance of MDR strains may cause a situation similar to the preantibiotic era and may necessitate the use of new antipseudomonal agents with alternative mechanisms of action or polymyxins despite their toxicity.

Pandrug resistant *P. aeruginosa* isolates, defined as resistant to carbapenems or to all antibiotics available for clinical use, are being reported with increasing frequency. Most cases are seen in patients who yielded a previous *P. aeruginosa* culture and had been treated with long courses of multiple antipseudomonal antibiotics.[139]

## *Acinetobacter baumannii*

*A. baumannii* has emerged as an opportunistic pathogen of particular importance among acutely ill patients. *A. baumannii* has been implicated in nosocomial infections including bacteremia, pneumonia, meningitis, UTIs, and skin and soft tissue

infections.[140] Outbreaks involving MDR strains have been reported among patients admitted to medical and surgical ICUs, including burn patients.[141] These outbreaks are usually associated with the spread of a unique strain and have been linked to a variety of fomites, primarily respiratory equipment, environmental surfaces such as computer keyboards and doorknobs, and definitely the hands of hospital personnel.[142–147] Multidrug resistance among *A. baumannii* has been associated with antibiotic selective pressure in the hospital environment and with an increased potential for epidemic behavior.[148–150] The ability to develop extremely rapid resistance makes *A. baumannii* infections very complicated. Susceptibility of *A. baumannii* to antimicrobials is considerably different among countries, among centers, and even among the wards of a given hospital. Sulbactam, supernormal doses of ampicillin–sulbactam, cilastin, polymyxin B, and newer quinolones such as clinafloxacin and garenoxacin along with other nonquinolone antibiotics and imipenem were reported to keep their efficacy against some resistant strains of *A. baumannii*.[141,151–154] Compliance with hand hygiene, strict patient isolation, and meticulous environmental cleaning has been integral in terminating *Acinetobacter* outbreaks.[147,155] It is specifically very important to act according to local surveillance in determining the most accurate therapy for *A. baumanii* infections.

### *Vancomycin-Resistant Enterococci*

In recent decades, enterococci have become important pathogens responsible for various infections, particularly those of nosocomial origin. They are intrinsically resistant to many antimicrobial agents and have shown a remarkable ability to become resistant to some other antibiotics, especially glycopeptides.[156] VRE have emerged as an important pathogen during the past 15 years in the United States.[157,158] Currently, most healthcare facilities in the United States have infection control programs that address VRE since infections with these pathogens are associated with high treatment costs and mortality rates.[159–161] Controlling the transmission of VRE within healthcare organization is a major focus of infection control programs. One important control measure is the identification of colonized patients.[162] These patients serve as reservoirs and facilitate VRE spread within hospitals. Current surveillance studies include monitoring patients on high-risk nursing units (i.e., ICUs and transplant units), however, these patients do not cover all the potential carriers. Lee et al. reported five VRE-harboring patients in non-high-risk groups through evaluation of all specimens, which are obtained for *C. difficile*. As all five patients had a history of hospitalization within 2 years, the authors advised screening all of patients hospitalized in the previous 2 years.[163]

## Rational Use of Antimicrobials

For selection of appropriate antibiotic treatment, the Council for Appropriate and Rational Antibiotic Therapy (CARAT) recommends determining whether a treatment choice is: (1) supported by clinical evidence, (2) likely

to provide therapeutic benefits, (3) safe, (4) an optimal drug for optimal duration, (5) cost-effective.

Overconsumption of antibiotics is linked to the emergence of resistance. Unfortunately, reducing prescription of antibiotics may not be enough to reduce resistance, unless it encompasses all classes simultaneously, since resistance to one antibiotic may be driven by exposure to another through the phenomenon of multidrug resistance. So it is clearly more reasonable to limit the use of antibiotics before the emergence of resistance, not after. Rational use of antimicrobials (using the correct drug by the best route in the right dose at optimum intervals for the appropriate period after an accurate diagnosis), regulation of over-the-counter drugs, preservation of existing agents, and development of new drugs are efforts of today's civilized population to overcome the increasing resistance among the microorganisms.[164,165]

In 1967, U.S. Surgeon General William H. Stewart declared that it was time to "close the book" on infectious diseases, but today's picture makes the following quote from Appelbaum et al. more reasonable: "The nature of the antimicrobial resistance means that treatment guidelines are ever changing; agents that were effective 10 years ago may well be less than optimal therapy today."[166]

Although antimicrobial resistance is increasing today, it is still preventable, before we find ourselves helpless like our ancestors in the preantibiotic era. Physicians must become aware of resistance patterns in their own communities and should take the required preventive measures in order to help control the rise in microbial resistance.

## *References*

1. Sefton AM. Mechanisms of antimicrobial resistance: Their clinical relevance in the new millennium. Drugs 2002;62:557–566.
2. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Infect Dis 1999;5:18–27.
3. Pieboji JG, Koulla-Shiro S, Ngassam P, Adiogo D, Njine T, Ndumbe P. Antimicrobial resistance of Gram-negative bacilli isolates from inpatients and outpatients at Yaounde Central Hospital, Cameroon. Int J Infect Dis 2004;8:147–154.
4. Cookson B. Infection and antimicrobial prescribing control in the new millennium: Nightmare or nirvana? J Clin Pathol 2000;53:66–70.
5. Gaynes RP. Surveillance of nosocomial infections: A fundamental ingredient for quality. Infect Control Hosp Epidemiol 1997;18:475–478.
6. Jarvis WR. Preventing the emergence of multidrug-resistant microorganisms through antimicrobial use controls: The complexity of the problem. Infect Control Hosp Epidemiol 1996;17:490–495.
7. Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant Staphylococcus aureus in U.S. hospitals, 1975–1991. Infect Control Hosp Epidemiol 1992;13: 582–586.
8. Morris JG, Shay DK, Hebden JN et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin: Establishment of endemicity in a university medical center. Ann Intern Med 1995;123:250–259.

9. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. JAMA 1996;275:234–240.
10. Centers for Disease Control and Prevention campaign to prevent antimicrobial resistance in health-care settings. MMWR 2002;51:343.
11. Alvarez-Lerma F, Palomar M, Grau S. Management of antimicrobial use in the intensive care unit. Drugs 2001;61:763–775.
12. Ruef C. Nosocomial infections in intensive care units. Infection 2005;3:105.
13. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: Self-reported incidence and associated costs Ann Epidemiol 2000;10:509–515.
14. Urinary tract infections and the cost of antimicrobial resistance: A special report, in Roberts WO (ed). Postgraduate Medicine. Minneapolis, MN, Healthcare Information Programs, McGraw–Hill Healthcare Information Group, 2001.
15. Gordon KA, Jones RN. SENTRY Participant Groups (Europe, Latin America, North America). Susceptibility patterns of orally administered antimicrobials among urinary tract infection pathogens from hospitalized patients in North America: Comparison report to Europe and Latin America. Results from the SENTRY Antimicrobial Surveillance Program (2000). Diagn Microbiol Infect Dis 2003;45:295–301.
16. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). Clin Infect Dis 1999;29:745–758.
17. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. J Gen Intern Med 1999;14:606–609.
18. Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. Mayo Clin Proc 2004;79:1048–1053.
19. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: A decision and cost analysis. Clin Infect Dis 2001;33:615–621.
20. Perfetto EM, Gondek K. Escherichia coli resistance in uncomplicated urinary tract infection: A model for determining when to change first-line empirical antibiotic choice. Manag Care Interface 2002;15:35–42.
21. Gilbert DN, Moellering RC Jr, Eliopoulos GM, Sande MA. The Sanford Guide to Antimicrobial Therapy, ed 34. Hyde Park, VT, Antimicrobial Therapy, Inc., 2004.
22. Muratani T, Matsumoto T. Bacterial resistance to antimicrobials in urinary isolates. Int J Antimicrob Agents 2004;24 Suppl 1:S28–S31.
23. Poiata A, Badicut I, Grigore L, Buiuc D. The frequency of in vitro resistance to fluoroquinolones among clinical isolates of Escherichia coli. Roum Arch Microbiol Immunol 2000;59: 63–69.
24. Andreu A, Alos JI, Goberdano M, Marco F, de la Rosa M, Garcia-Rodriguez JA. Etiology and antimicrobial susceptibility among uropathogens causing community-acquired lower urinary tract infections: A nationwide surveillance study. Enferm Infecc Microbiol Clin 2005;23:4–9.
25. Nicolle L. Best pharmacological practice: Urinary tract infections. Expert Opin Pharmacother 2003;4:693–704.
26. Kahlmeter G, Menday P, Cars O. Non-hospital antimicrobial usage and resistance in community acquired Escherichia coli urinary tract infection. J Antimicrob Chemother 2003;52:1005–1010.
27. Richard P, Delangle MH, Merrien D, et al. Fluoroquinolone use and fluoroquinolone resistance: Is there an association? Clin Infect Dis 1994;19:54–59.

28. Kresken M, Wiedemann B. Development of resistance to nalidixic acid and the fluoroquinolones after the introduction of norfloxacin and ofloxacin. Antimicrob Agents Chemother 1988;32:1285–1288.
29. Muder RR, Brennen C, Goetz AM, Wagener MM, Rihs JD. Association with prior fluoroquinolone therapy of widespread ciprofloxacin resistance among gram-negative isolates in a Veterans Affairs medical center. Antimicrob Agents Chemother 1991;35:256–258.
30. Pena C, Albareda JM, Pallares R, Pujol M, Tubau F, Ariza J. Relationship between quinolone use and emergence of ciprofloxacin-resistant Escherichia coli in bloodstream infections. Antimicrob Agents Chemother 1995;39:520–524.
31. Nicolle LE. Urinary tract infection: Traditional pharmacologic therapies. Am J Med 2002;113(suppl 1A):35S–44S.
32. Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: A nationwide analysis. Clin Infect Dis 2001;33:89–94.
33. Aubert G, Levy PP, Ros A, Meley R, Bourge A, Dorche G. Changes in the sensitivity of urinary pathogens to quinolones between 1987 and 1990 in France. Eur J Clin Microbiol Infect Dis 1992;11:475–477.
34. Rüden H, Gastmeier P, Daschner FD, Schumacher M. Nosocomial and community-acquired infections in Germany. Summary of the results of first national prevalence study (NIDEP). Infection 1997;25:199–202.
35. Gastmeier P, Kampf G, Wischnewski N, et al. Prevalence of nosocomial infections in representative German hospitals. J Hosp Infect 1998;38:37–49.
36. Maki DG, Tambyah PA. Engineering out the risk of infection with urinary catheters. Emerg Infect Dis 2001;7:342–347.
37. Perrin M, Donnio PY, Heurtin-Lecorre C, Travert MF, Avril L. Comparative antimicrobial resistance and genomic diversity of Escherichia coli isolated from the urinary tract infections in the community and in hospitals. J Hosp Infect 1999:41;273–279.
38. Mathai D, Jones RN, Pfaller MA. Epidemiology and frequency of resistance among pathogens causing urinary tract infections in 1510 hospitalized patients: A report from the SENTRY Antimicrobial Surveillance Program (North America). Diagn Microbiol Infect Dis 2001;40:129–136.
39. Bouza E, San Juan R, Muñoz P, Voss A, Kluytmans J: Co-operative Group of the European Study Group on Nosocomial Infections. A European perspective on nosocomial urinary tract infections I. Report on the microbiology workload, etiology and antimicrobial susceptibility (ESGNI-003 study). European Study Group on Nosocomial Infections. Clin Microbiol Infect 2001;7:523–531.
40. Johansen TE. Nosocomially acquired urinary tract infections in urology departments. Why an international prevalence study is needed in urology. Int J Antimicrob Agents 2004;23(suppl 1):S30–S34.
41. Wagenlehner FM, Weidner W, Naber KG. Emergence of antibiotic resistance amongst hospital-acquired urinary tract infections and pharmacokinetic/pharmacodynamic considerations. J Hosp Infect 2005;60:191–200.
42. Morgan MA, Brock N, Schneider S, et al. β-Lactam resistance in *Escherichia coli* and *Klebsiella pneumonia*: Laboratory detection and patient characteristics [abstr], in: Program and Abstracts of 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, American Society for Microbiology, 1998, p 143.
43. Babni GS, Hall LMC, Yuamn M, et al. Changes in the epidemiology of *Klebsiella* species: ESBL producers collected from intensive care units in 1994 and

1997–1998 [abstr], in: Program and Abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, American Society for Microbiology, 2000, p 122.
44. Einhorn AE, Neuhauser MM, Bearden DT, Quinn JP, Pendland SL. Extended-spectrum β-lactamases: Frequency, risk factors and outcomes. Pharmacotherapy 2002;22:14–20.
45. Rice LB. Successful interventions for gram-negative resistance to extended spectrum β-lactam antibiotics. Pharmacotherapy 1999;19:120S–128S.
46. Diekema DJ, Pfaller MA, Jones RA, et al. Survey of blood stream infections due to gram-negative bacilli: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin Infect Dis 1999;29:595–607.
47. D'Agata EM, Venkataraman L, DeGirolami P, et al. Colonization with broad-spectrum cephalosporin-resistant gram-negative bacilli in intensive care units during a nonoutbreak period: Prevalence, risk factors, and rate of infection. Crit Care Med 1999;27:1090–1095.
48. Schiappa DA, Hayden MK, Matushek MG, et al. Ceftazidime resistant Klebsiella pneumonia and Escherichia coli bloodstream infection: A case control and molecular epidemiologic investigation. J Infect Dis 1996;174:529–536.
49. Lautenbach E, Patel JB, Bilker WB, Edelstein PH, Fishman NO. Extended-spectrum β-lactamase–producing Escherichia coli and Klebsiella pneumonia: Risk factors for infection and impact of resistance on outcomes. Clin Infect Dis 2001;32:1162–1171.
50. Wiener J, Quinn JP, Bradford PA, et al. Multiple antibiotic resistant Klebsiella and Escherichia coli in nursing homes. JAMA 1999;281:517–523.
51. Colodner R, Rock W, Chazan B, et al. Risk factors for the development of extended-spectrum β-lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis 2004;23:163–167.
52. Borer A, Gilad J, Menashe G, Peled N, Riesenberg K, Schlaeffer F. Extended-spectrum β-lactamase-producing Enterobacteriaceae strains in community-acquired bacteremia in southern Israel. Med Sci Monitor 2002;8:CR44–CR7.
53. Munday CJ, Whitehead GM, Todd NJ, Campbell M, Hawkey PM. Predominance and genetic diversity of community- and hospital-acquired CTX-M extended-spectrum β-lactamases in York, UK. J Antimicrobiol Chemother 2004;54:628–633.
54. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ, for the Infectious Diseases Society of America. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347–382.
55. Niederman MS, Mandell LA, Anzueto A, et al, for the Ad-hoc Sub-committee of the assembly on microbiology, tuberculosis and pulmonary infections. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163:1730–1754.
56. Sahm DF. Resistance issues and community-acquired respiratory infections. Clin Cornerstone 2003;Suppl 3:S4–S11.
57. Feikin DR, Schuchat A, Kolczak M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance, 1995–1997. Am J Public Health 2000; 90: 223–229.
58. Cross JT Jr, Campbell GD Jr. Drug-resistant pathogens in community- and hospital-acquired pneumonia. Clin Chest Med 1999;20:499–506.
59. Whitney CG, Farley MM, Hadler J, et al. Active Bacterial Core Surveillance program of the Emerging Infections Program Network. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med 2000;343:1917–1924.

60. Baquero F. Pneumococcal resistance to beta-lactam antibiotics: A global geographic overview. Microb Drug Resist 1995;1:115–120.
61. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group. Arch Intern Med 2000;160:1399–1408.
62. Doern GV, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of Streptococcus pneumoniae in North America: 1997 results from the SENTRY antimicrobial surveillance program. Clin Infect Dis 1998; 27:764–770.
63. Segreti J, House HR, Siegel RE. Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. Am J Med 2005;118 Suppl 7A:21S–28S.
64. Jones RN, Mandell LA. Fluoroquinolones for the treatment of outpatient community-acquired pneumonia. Diagn Microbiol Infect Dis 2002;44:69–76.
65. Doern GV, Richter SS, Miller A, et al. Antimicrobial resistance among Streptococcus pneumoniae in the United States: Have we begun to turn corner on resistance to certain antimicrobial classes? Clin Infect Dis 2005;41:139–149.
66. Abdel-Rahman EM, Ismael NA, Dixon RA. Antibiotic resistance and prevalence of β-lactamase in Haemophilus influenza isolates—A surveillance study of patients with respiratory infection in Saudi Arabia. Diagn Microbiol Infect Dis 2000;36:203–208.
67. Doern GV, Pfaller MA, Erwin ME, Brueggemann AB, Jones RN. The prevalence of fluoroquinolone resistance among clinically significant respiratory tract isolates of Streptococcus pneumoniae in the United States and Canada—1997 results from the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis 1998; 32:313–316.
68. Brown SD, Rybak MJ. Antimicrobial susceptibility of Streptococcus pneumoniae, Streptococcus pyogenes and Haemophilus influenzae collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study. J Antimicrob Chemother 2004;54 Supp1:i7–i15.
69. Richter SS, Heilmann KP, Beekmann SE, Miller NJ, Rice CL, Doern GV. The molecular epidemiology of Streptococcus pneumoniae with quinolone resistance mutations. Clin Infect Dis 2005;40:225–235.
70. Bhavnani SM, Hammel JP, Jones RN, Ambrose PG. Relationship between increased levofloxacin use and decreased susceptibility of Streptococcus pneumoniae in the United States. Diagn Microbiol Infect Dis 2005;51:31–37.
71. Grossman RF. Guidelines for the treatment of acute exacerbations of chronic bronchitis. Chest 1997; 112(6 Suppl):310S–313S.
72. Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H. Infective exacerbations of chronic bronchitis: Relation between bacteriologic etiology and lung infection. Chest 1998;113:1542–1548.
73. Pfaller MA, Ehrhardt AF, Jones RN. Frequency of pathogen occurrence and antimicrobial susceptibility among community-acquired respiratory infections in the respiratory surveillance program study: Microbiology from the medical office practice environment. Am J Med 2001;111 Suppl 9A:4S–12S.
74. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patient with pulmonary infiltrates in the intensive care unit: A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 2000;162:505–511.

75. McEachern R, Campbell GD Jr. Hospital-acquired pneumonia: Epidemiology, etiology, and treatment. Infect Dis Clin North Am 1998;12:761–779.
76. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator associated, and healthcare associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
77. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: A randomized trial. JAMA 2000;283:1583–1590.
78. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. Lancet 2003; 362:887–899.
79. Espinal MA. The global situation of MDR-TB. Tuberculosis 2003;83:44–51.
80. Centers for Disease Control and Prevention (CDC). Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR 2006;55:301–305.
81. Pablos-Mendez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis drug resistance, 1994–1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 1998;338:1641–1649.
82. Di Perri G, Bonora S. Which agents should we use for the treatment of multidrug-resistant Mycobacterium tuberculosis? J Antimicrob Chemother 2004;54:593–602.
83. Lalloo UG, Naidoo R, Ambaram A. Recent advances in the medical and surgical treatment of multi-drug resistant tuberculosis. Curr Opin Pulm Med 2006;12:179–185.
84. Diekema DJ, Pfaller MA, Schmitz FJ, et al. and the SENTRY participants. Survey of infections due to Staphylococcus species: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Wertern Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 2001;32 Suppl 2:S114–S132.
85. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867–903.
86. Shorr AF, Combes A, Kollef MH, Chastre J. Methicillin-resistant Staphylococcus aureus prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. Crit Care Med 2006;34:700–706.
87. Archer GL, Climo MW. Antimicrobial susceptibility of coagulase-negative staphylococci. Antimicrob Agents Chemother 1994;38:2231–2237.
88. Lowy FD. Staphylococcus aureus infections. N Engl J Med 1998;339: 20–32.
89. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992–June 2001, issued August 2001. Am J Infect Control 2001; 29:404–421.
90. Barber M. Methicillin resistant staphylococci. J Clin Pathol 1961;14;385–393.
91. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–317.
92. Ho M, McDonald LC, Lauderdale TL, et al. Surveillance of antibiotic resistance in Taiwan, 1998. J Microbiol Immunol Infect 1999;32:239–249.
93. Brumfitt W, Hamilton-Miller J. Methicillin resistant Staphylococcus aureus. N Engl J Med 1989;320:1188–1196.
94. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carnelli Y. Comparison of mortality associated with methicillin-resistant and methicillin susceptible Staphylococcus aureus bacteremia: A meta analysis. Clin Infect Dis 2003;36:53–59.

95. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant Staphylococcus aureus bacteremia: A meta-analysis. Med J Aust 2001;175:264–267.
96. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997;40:135–136.
97. Sieradzki K, Roberts RB, Haber SW, Tomasz A. The development of vancomycin resistance in a patient with methicillin-resistant Staphylococcus aureus infection. N Engl J Med 1999;340:517–523.
98. Appelbaum PC. The emergence of vancomycin-intermediate and vancomycin resistant Staphylococcus aureus. Clin Microbiol Infect 2006;12 Suppl 1:16–23.
99. Segreti J. Efficacy of current agents used in the treatment of Gram-positive infections and the consequences of resistance. Clin Microbiol Infect 2005;11:29–35.
100. Tsiodras S, Gold HS, Sakoulas G, et al. Linezolid resistance in a clinical isolate of Staphylococcus aureus. Lancet 2001;358:207–208.
101. Verhoef J, Beaujean D, Blok H, et al. A Dutch approach to methicillin resistant Staphylococcus aureus. Eur J Clin Microbiol Infect Dis 1999;18:461–466.
102. Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current microbial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. Ann Clin Microbiol Antimicrobiol 2006;5:2.
103. Centers for Disease Control. Community-acquired methicillin-resistant Staphylococcus aureus infections: Michigan. MMWR 1981;30:185–187.
104. Saravolatz LD, Pohlod DJ, Arking LM. Community-acquired methicillin-resistant Staphylococcus aureus infections: A new source for nosocomial outbreaks. Ann Intern Med 1982;97:325–329.
105. From the Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant Staphylococcus aureus—Minnesota and North Dakota, 1997–1999. JAMA 1999;282:1123–1125.
106. http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca_clinicians.html#4. Accessed online April 26,2006.
107. Murray RJ, Lim TT, Pearson JC, Grubb WB, Lum GD. Community-onset methicillin resistant Staphylococcus aureus bacteremia in northern Australia. Int J Infect Dis 2004;8:275–283.
108. Hidron AI, Kourbatova E, Halvosa JS, et al. Risk factors for colonization with methicillin-resistant Staphylococcus aureus (MRSA) in patients admitted to an urban hospital: Emergence of community-associated MRSA nasal carriage. Clin Infect Dis 2005;41:159–166.
109. Rezende NA, Blumberg HM, Metzger BS, Larsen NM, Ray SM, McGowan JE Jr. Risk factors for methicillin-resistance among patients with Staphylococcus aureus bacteremia at the time of hospital admission. Am J Med Sci 2002; 323: 117–123.
110. Calfee DP, Durbin LJ, Germanson TP, Toney DM, Smith EB, Farr BM. Spread of methicillin resistant Staphylococcus aureus (MRSA) among household contacts of individuals with nosocomially acquired MRSA. Infect Control Hosp Epidemiol 2003;24:422–426.
111. Maltezou HC, Giamarellou H. Community-acquired methicillin-resistant Staphylococcus aureus infections. Int J Antimicrob Agents 2006;27:87–96.
112. Anonymous. National Nosocomial Infections Surveillance (NNIS) System Report: Data summary from October 1986 to April 1998, issued June 1998. Am J Infect Control 1988;26:522–533.

113. Anonymous. National Nosocomial Infections Surveillance (NNIS) Report, data summary from October 1986 to April 1996, issued May 1996. Am J Infect Control 1996;24:380–388.
114. Bouza E, Burillo A, Munoz P. Catheter-related infections: Diagnosis and intravascular treatment. Clin Microbiol Infect 2002;8:265–274.
115. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274:639–644.
116. Crouch Brewer S, Wunderink RG, Jones CB, Leeper KV Jr. Ventilator-associated pneumonia due to Pseudomonas aeruginosa. Chest 1996;109:1019–1029.
117. Mayhall CG. Nosocomial pneumonia. Diagnosis and prevention. Infect Dis Clin North Am 1997;11:427–457.
118. Rello J, Rue M, Jubert P, et al. Survival in patients with nosocomial pneumonia: Impact of the severity of illness and the etiologic agent. Crit Care Med 1997;25:1862–1867.
119. Bodey GP, Jadeja L, Elting L. Pseudomonas bacteremia. Retrospective analysis of 410 episodes. Arch Intern Med 1985;145:1621–1629.
120. Gallagher PG, Watanakunakorn C. Pseudomonas bacteremia in a community teaching hospital 1980–1984. Rev Infect Dis 1989;11:846–852.
121. Siegman-Igra Y, Ravona R, Primerman H, Giladi M. Pseudomonas aeruginosa bacteremia: An analysis of 123 episodes, with particular emphasis on the effect of antimicrobial therapy. Int J Infect Dis 1998;2:211–215.
122. Pollack M. Pseudomonas aeruginosa, in Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, ed 5. Philadelphia, Churchill Livingstone, 2000, pp 2310–2335.
123. Koll BS, Brown AE. The changing epidemiology of infections at cancer hospitals. Clin Infect Dis 1993;17 Suppl 2:S322-S328.
124. Aquino VM, Pappo A, Buchanan GR, Tkaczewski I, Mustafa MM. The changing epidemiology of bacteremia in neutropenic children with cancer. Pediatr Infect Dis J 1995;14:140–143.
125. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741–1751.
126. Pizzo PA. Fever in immunocompromised patients. N Engl J Med 1999;341:893–900.
127. Giamarellou H, Antoniadou A. Antipseudomonal antibiotics. Med Clin North Am 2001;85:19–42.
128. Jones RN, Beach ML, Pfaller MA. Spectrum and activity of the three contemporary fluoroquinolones tested against Pseudomonas aeruginosa isolates from the urinary tract infections in the SENTRY Antimicrobial Surveillance Program (Europe and the Americas: 2000): More alike than different! Diagn Microbiol Infect Dis 2001;41:161–163.
129. Giamarellou H. Prescribing guidelines for severe Pseudomonas infections. J Antimicrob Chemother 2002;49:229–233.
130. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU settings. Chest 2000;118: 146–155.
131. Jones RN, Kirby JT, Beach ML, Biedenbach DJ, Pfaller MA. Geographic variations in activity of broad spectrum β-lactams against Pseudomonas aeruginosa: Summary of worldwide SENTRY antimicrobial surveillance program (1997–2000). Diagn Microbiol Infect Dis 2002;43:239–243.

132. Karlowsky JA, Draghi DC, Jones ME, Thornsberry C, Friedland IR, Sahm DF. Surveillance for antimicrobial susceptibility among clinical isolates of Pseudomonas aeruginosa and Acinetobacter baumannii from the hospitalized patients in the United States, 1998–2001. Antimicrob Agents Chemother 2003;47:1681–1688.
133. Mendes C, Turner PJ. MYSTIC Study Group (Europe). Unit differences in pathogen occurrence arising from the MYSTIC program European database (1997–2000). Diagn Microbiol Infect Dis 2001;41:191–196.
134. Hanberger H, Diekema D, Fluit A et al. Surveillance of antibiotic resistance in European ICUs. J Hosp Infect 2001;48:161–176.
135. Friedland I, Stinson L, Ikaiddi M, Harm S, Woods GL. Phenotypic antimicrobial resistance patterns in Pseudomonas aeruginosa and Acinetobacter: Results of a Multicenter Intensive Care Unit Surveillance Study, 1995–2000. Diagn Microbiol Infect Dis 2003;45:245–250.
136. Pfaller MA, Jones RN, Biedenbach DJ. MYSTIC Program Study Group. Antimicrobial resistance trends in medical centers using carbapenems: Report of 1999 and 2000 results from the MYSTIC Program (USA). Diagn Microbiol Infect Dis 2001;41:177–182.
137. Gales AC, Jones RN, Turnidge J, Rennie R, Ramphal R. Characterization of Pseudomonas aeruginosa isolates: Occurrence rates, antimicrobial susceptibility patterns, and molecular typing in the global SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 2001;32 Suppl 2:S146–S155.
138. Livermore DM. Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: Our worst nightmare? Clin Infect Dis 2002;34:634–640.
139. Wang CY, Jerng JS, Cheng KY, et al. Pandrug-resistant *Pseudomonas aeruginosa* among hospitalized patients: Clinical features, risk factors and outcomes. Clin Microbiol Infect 2006;12:63–68.
140. Zeana C, Larson E, Sahni J, Bayuga SJ, Wu F, Della-Latta P. The epidemiology of multidrug-resistant Acinetobacter baumannii: Does the community represent a reservoir? Infect Control Hosp Epidemiol 2003;24:275–279.
141. Maslow JN, Glaze T, Adams P, Lataillade M. Concurrent outbreak of multidrug resistant and susceptible subclones of Acinetobacter baumannii affecting different wards of a single hospital. Infect Control Hosp Epidemiol 2005;26:69–75.
142. Go ES, Urban C, Burns J, et al. Clinical and molecular epidemiology of Acinetobacter infections sensitive only to polymyxin B and sulbactam. Lancet 1994: 344: 1329–1332.
143. D'Agata EM, Thayer V, Schaffner W. Outbreak of Acinetobacter baumannii: The importance of cross-transmission. Infect Control Hosp Epidemiol 2000;21:588–591.
144. Husni RN, Goldstein LS, Arroliga AC, et al. Risk factors for an outbreak of multidrug resistant Acinetobacter nosocomial pneumonia among intubated patients. Chest 1999;115:1378–1382.
145. Cox TR, Roland WE, Dolan ME. Ventilator related Acinetobacter outbreak in an intensive care unit. Mil Med 1998;163:389–391.
146. Roberts SA, Findlay R, Lang SD. Investigation of an outbreak of multi-drug resistant Acinetobacter baumannii in an intensive care burns unit. J Hosp Infect 2001; 48:228–232.
147. Neely AN, Maley MP, Warden GD. Computer keyboards as reservoirs for Acinetobacter baumannii in a burn hospital. Clin Infect Dis 1999;29:1358–1360.
148. Manikal VM, Landman D, Saurina G, Odyna E, Lal H, Quale J. Endemic carbapenem-resistant Acinetobacter species in Brooklyn, New York: City prevalence, interinstitutional spread, and relation to antibiotic use. Clin Infect Dis 2000:31:101–106.

149. Rahal JJ, Urban C, Segal-Maurer S. Nosocomial antibiotic resistance in multiple gram-negative species: Experience at one hospital with squeezing the resistance balloon at multiple sites. Clin Infect Dis 2002;34:499–503.
150. Dijkshoorn L, Aucken H, Gerner-Smidt P, et al. Comparison of outbreak and nonoutbreak Acinetobacter baumannii strains by genotypic and phenotypic methods. J Clin Microbiol 1996;34:1519–1525.
151. Cisneros JM, Rodriguez-Bano J. Nosocomial bacteremia due to Acinetobacter baumannii: Epidemiology, clinical features and treatment. Clin Microbiol Infect 2002;8:687–693.
152. Cawley MJ, Suh C, Lee S, Ackerman BH. Nontraditional dosing of ampicillin-sulbactam for multidrug resistant Acinetobacter baumannii meningitis. Pharmacotherapy 2002;22:527–532.
153. Nikolaidis P, Metallidis S, Kollaras P, Tsona A, Koumedaki E, Tsaousoglu D. In vitro activity of clinafloxacin compared to ciprofloxacin against Acinetobacter baumannii strains isolated from intensive care unit patients. J Chemother 2002;14:234–236.
154. Fung-Tomc JC, Gradelski E, Valera L, Huczko E, Bonner DP. Synergistic activity of the novel des-fluoro(6) quinolone garenfloxacin (BMS-284756) in combination with other antimicrobial agents against Pseudomonas aeruginosa and related species. Int J Antimicrob Agents 2002;20:57–60.
155. Jellison TK, McKinnon PS, Rybak MJ. Epidemiology, resistance and outcome of Acinetobacter baumannii bacteremia treated with imipenem-cilastatin or ampicillin-sulbactam. Pharmacotherapy 2001;21:142–148.
156. Barisic Z, Punda-Polic V. Antibiotic resistance among enterococcal strains isolated from clinical specimens. Int J Antimicrob Agents 2000;16:65–68.
157. Chavers LS, Moser SA, Benjamin WH, et al. Vancomycin-resistant enterococci: 15 years and counting. J Hosp Infect 2003;53:159–171.
158. Murray BE. Vancomycin-resistant enterococcal infections. N Engl J Med 2000; 342:710–721.
159. Linden PK, Pasculle AW, Manez R, et al. Differences in outcomes for patients with bacteremia due to vancomycin-resistant Enterococcus faecium or vancomycin-susceptible *E. faecium.* Clin Infect Dis 1996;22:663–670.
160. Lodise TP, McKinnon PS, Tam VH, Rybak MJ. Clinical outcomes for patients with bacteremia caused by vancomycin resistant Enterococcus in a level 1 trauma center. Clin Infect Dis 2002;34:922–929.
161. Stosor V, Peterson LR, Postelnick M, Noskin GA. Enterococcus faecium bacteremia: Does vancomycin resistance make a difference? Arch Intern Med 1998;158:522–527.
162. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug resistant Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol 2003;24:362–386.
163. Lee TA, Hacek DM, Stroupe KT, Collins SM, Peterson LR. Three surveillance strategies for vancomycin-resistant enterococci in hospitalized patients: Detection of colonization efficiency and a cost-effectiveness model. Infect Control Hosp Epidemiol 2005;26:39–46.
164. Holloway K. Antimicrobial resistance: The facts. Essential Drug Monitor, WHO 2000;28–29:7–8.
165. Sharma R, Sharma CL, Kapoor B. Antibacterial resistance: Current problems and possible solutions. Indian J Med Sci 2005;59:120–129.
166. Appelbaum PC, Gillespie SH, Burley CJ, Tillotson GS. Antimicrobial selection for community-acquired lower respiratory tract infections in the 21st century: A review of gemifloxacin. Int J Antimicrob Agents 2004;23:533–546.

*This page intentionally blank*

# Chapter 9
# Fighting Antimicrobial Resistance in the Mediterranean Region

Michael A. Borg

## Introduction

The Mediterranean is a heterogeneous region composed of 20 countries which vary substantially in terms of size, population, and culture. More importantly, the individual nations differ substantially in their socioeconomic development varying by a factor of 7.7 from the country with the highest GDP per capita (France, $29,900) and the one with the lowest (Egypt, $3900) (CIA World Fact Book, 2005). This difference undoubtedly translates itself into varying levels of healthcare provision and should have a direct impact on the individual nations' capacities in addressing the challenge of antimicrobial resistance. Nevertheless, despite this wide disparity in resources, the epidemiology of antimicrobial resistance throughout the region shows remarkable similarity.

## Regional Epidemiology

Reports suggesting a high level of antimicrobial resistance in important pathogenic bacteria within countries of the Mediterranean region have been made for a number of years (Gür and Unal 2001). In addition to epidemiological surveys at individual center and country level, a number of studies have provided useful and comparable intercountry data, particularly from the European zone. Such studies have often pinpointed an increased level of resistance in their Mediterranean participants. The Alexander project highlighted a high prevalence of penicillin resistance among isolates of *Streptococcus pneumoniae* in France and Spain (Schito et al. 2000). Increased quinolone resistance was observed by the SENTRY project in urinary tract isolates from Italy, France, and Spain (Fluit et al. 2000). Extended-spectrum β-lactamases were reported to be common from centers in Italy and Turkey participating in the MYSTIC study (Jones et al. 2003).

Since 1999, the European Antimicrobial Resistance Surveillance System (EARSS) [www.earss.rivm.nl] has been collecting susceptibility test results from invasive strains of *Staphylococcus aureus, S. pneumoniae, Escherichia coli,*

*Enterococcus faecium* and *faecalis* which are routinely isolated from clinical samples of blood and cerebrospinal fluid in the participating laboratories. These laboratories are asked to send information only about the first strain isolated from each patient and to follow their routine procedures and breakpoints, which in 78% of participants were based on CLSI (formerly NCCLS) guidelines (EARSS report 2004). The same methodology has been adopted by another study, Antibiotic Resistance in the Mediterranean region (ARMed) [www.slh.gov.mt/armed], which has concentrated on the countries in the southern and eastern Mediterranean (Borg et al. 2006). As a result of the identical methodology used by both networks, it is now possible to depict a comparable epidemiological picture of antimicrobial resistance within the whole Mediterranean region.

The data from these two networks seem to support reports from earlier individual surveys and confirm a high prevalence of resistance within their Mediterranean participants. This is particularly the case with methicillin-resistant *Staphylococcus aureus*. (MRSA) where, other than Portugal, the United Kingdom, and Ireland, the highest incidence rates were identified from the Mediterranean participants (Figure 9.1). Proportions of MRSA blood culture isolates among the Mediterranean countries in EARSS in 2004 ranged from 11.8% in Slovenia to 56.4% in Malta. In fact, all the countries in the region (except for Slovenia) exhibited proportions in

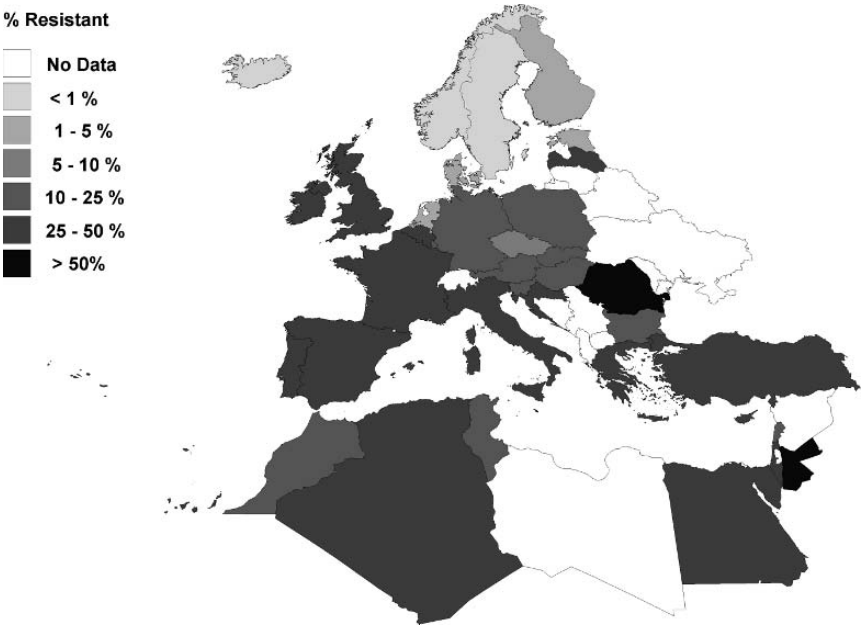



FIGURE 9.1. Invasive isolates of *Staphylococcus aureus* resistant to methicillin (MRSA) reported by laboratories participating in the EARSS and ARMed surveillance networks in 2004.

excess of 25%. In addition, the situation seems to be deteriorating. Significant increases in methicillin-resistance trends from 1999 to 2004 have been reported from the EARSS participating laboratories in Spain, Croatia, and Italy. On the other hand, France and Slovenia managed to show a decrease in these trends, the only participating countries in the network to show such a reduction. ARMed results for the same time period were reasonably similar, ranging between 18.3% in Tunisia and 61% in Jordan. The combined results of the two comparable studies would therefore appear to indicate the serious extent of the problem of MRSA among clinical isolates within Mediterranean countries. This is put into clearer focus when comparing the results with those originating from laboratories in the north and center of Europe. Neither study identified relevant reports of glycopeptide resistance among *S. aureus* strains but vancomycin resistance in excess of 5% was identified in Italy, Greece, and Israel within *E. faecalis* and *E. faecium* isolates.

Indications of resistance among strains of *S. pneumoniae* within Mediterranean countries are not new. Data from the Alexander Project (Felmingham and Gruneberg 1996) identified the Mediterranean participants in the study as having the highest resistance for penicillin, reaching over 50% in isolates from France and more than 30% in Greece and Israel. More recent data from EARSS have confirmed this initial picture (Figure 9.2). The overall majority

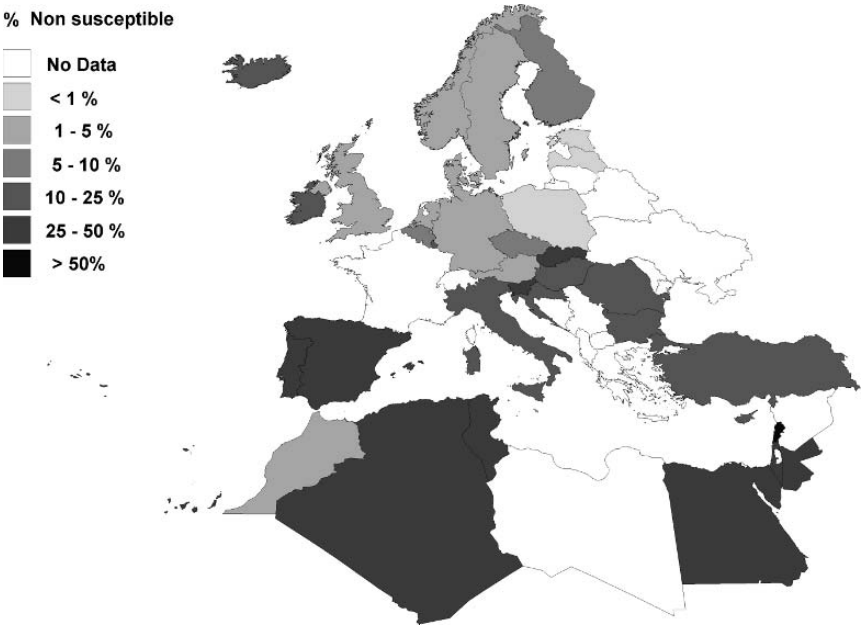



FIGURE 9.2. Invasive isolates of *Streptococcus pneumoniae* nonsusceptible to penicillin (PNSP) reported by laboratories participating in the EARSS and ARMed surveillance networks in 2004.

of participating countries from the region reported nonsusceptibility rates in excess of 10% for both penicillin and erythromycin, reaching 25% in Spain, France, Slovenia, and Israel. Furthermore, rates of full penicillin resistance were observed to significantly increase within Israel, Italy, and Slovenia over the years of EARSS data collection. In addition to penicillin nonsusceptibility, an additional burden seems to be posed by macrolide resistance, even in countries such as Italy, Malta, and Cyprus where penicillin susceptibility remains high (Figure 9.3). Outside of the region Europe, penicillin resistance in pneumococci appears to be also relevant in the southern and eastern countries. ARMed participating laboratories also reported penicillin nonsusceptibility levels which are quite similar to northern counterparts. It is interesting to note, however, that, contrary to data from the European countries of the region where macrolide resistance in pneumococci often exceeds that of penicillin (Bronzwaer 2003), erythromycin nonsusceptibility appears to be less prevalent in the southeastern Mediterranean countries.

Resistance seems to be equally relevant in Gram negative bacteria, especially enteric pathogens. Multiresistant *Salmonella* and *Shigella* infections have been described from various countries including Spain, Algeria, Israel,

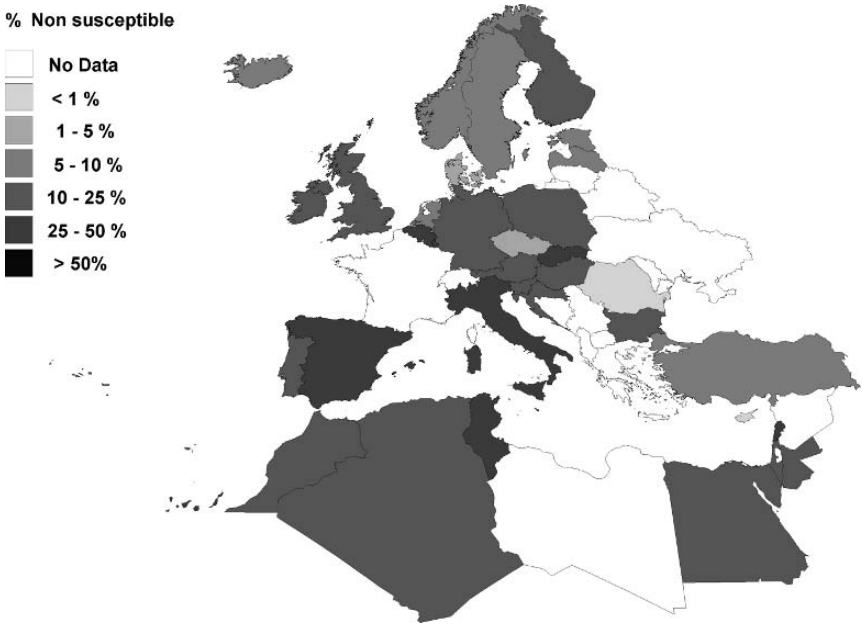



FIGURE 9.3. Invasive isolates of *Streptococcus pneumoniae* resistant to erythromycin reported by laboratories participating in the EARSS and ARMed surveillance networks in 2004.

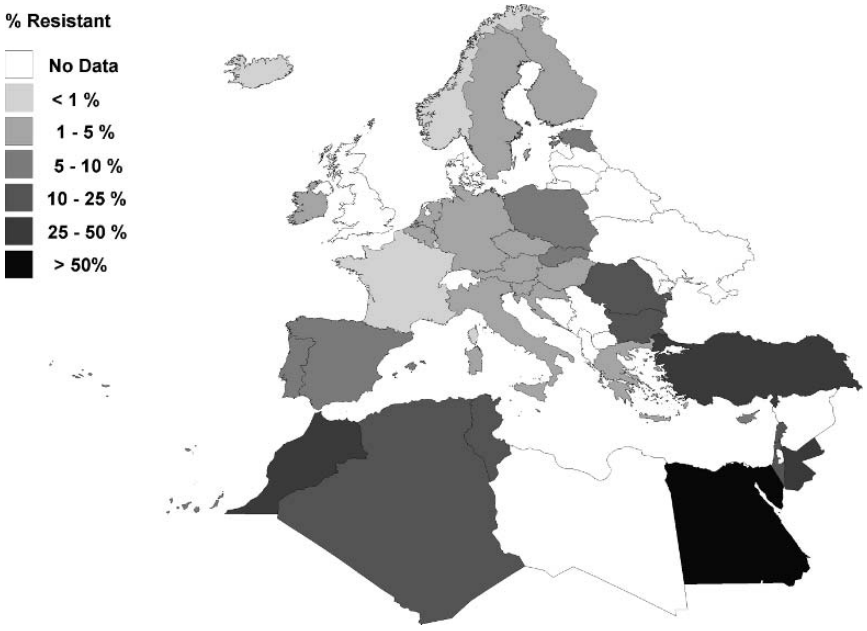



FIGURE 9.4. Invasive isolates of *Escherichia coli* resistant to third-generation cephalosporins reported by laboratories participating in the EARSS and ARMed surveillance networks in 2004.

Turkey, Greece, and Tunisia (Gür and Unal 2001). Of possibly greater concern is the emergence of extended spectrum β-lactamase in recent years, even within pathogens such as *E. coli* which are not normally associated with high levels of ESBL production. ARMed resistance rates toward third-generation cephalosporins in the eastern Mediterranean showed average proportions in excess of 20% (Figure 9.4). Egyptian hospitals in the study reported 72% resistance to third generation cephalosporins which is one of the highest figures recorded for this resistance trait. Nevertheless, indications of high-level resistance within Gram-negative pathogens in this region are not new. Bouchillon and colleagues (2004), studying isolates from 38 centers in 17 countries, reported the incidence of ESBL production in Enterobacteriacae to be at its highest in their Egyptian centers at 38.5%. El Kholy et al. (2003) noted that 62% of *E. coli* isolated from blood cultures in three Cairo hospitals were nonsusceptible to ceftazidime. The same countries also show high levels of resistance to fluoroquinolones in excess of 25%. In the European countries, ESBL production in *E. coli* seems to be less acute and resistance in this species tends to be confined to fluoroquinolones, particularly in Malta, Spain, and Italy (Figure 9.5).

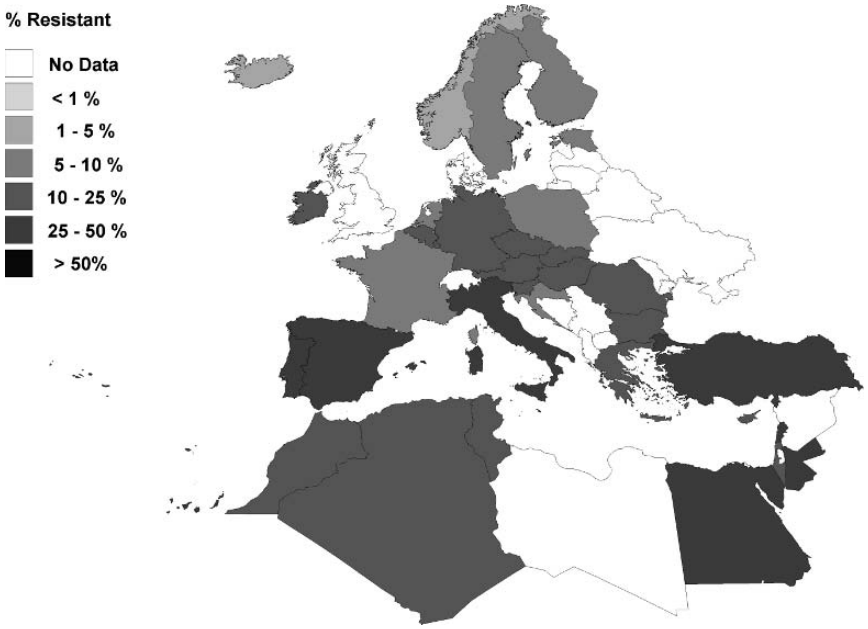



FIGURE 9.5. Invasive isolates of *Escherichia coli* resistant to fluoroquinolones reported by laboratories participating in the EARSS and ARMed surveillance networks in 2004.

## Antibiotic Use

In the light of this epidemiological evidence indicating a high prevalence of antimicrobial resistance in most important pathogens throughout the Mediterranean, it is important to assess possible factors which may be contributing to this state of affairs, particularly antibiotic consumption and infection control. As with data on resistance, information on antibiotic use within the countries of the region has, in the past, been scanty. However, recently established networks and studies have again helped to improve our understanding considerably. Feedback from the European Surveillance of Antimicrobial Consumption (ESAC) network [www.ua.ac.be/esac] suggests regional clustering patterns in antibiotic consumption within ambulatory care in Europe, being lowest in the north, moderate in the east, and highest in the south—particularly in France, Greece, and Italy. The ambulatory care consumption of antibiotics in France was reported to be 3.2 times higher than that in the Netherlands (Goossens et al. 2005). These statistically significant regional differences apply both to total consumption of antibiotics as well as to individual antimicrobials such as the wide spectrum penicillins. In addition to overall consumption, it would also seem that inappropriate use of antimicrobials may be a factor in the management of ambulatory care infections

in the Mediterranean countries of Europe. The same publication noted a high seasonal fluctuation within southern European countries well in excess of 30% in ambulatory care consumption between the first and fourth quarter of the year as compared to less than 25% in the northern countries. One reason proposed by the authors for this difference centers on cultural differences and diagnostic labeling. They suggest that in the countries with higher fluctuations there is a greater tendency for respiratory infections to be labeled as potentially bacterial in origin. On the contrary, in the countries where seasonal fluctuations are smaller, physicians often determine similar infections as viral colds or influenza, hence not requiring treatment. Goossens and colleagues (2005) have also suggested a correlation between the use of antibiotics in ambulatory care in European countries and the incidence of resistance, specifically a link between outpatient use of penicillins and incidence of non-penicillin-susceptible *S. pneumoniae*. The same association was put forward previously by Bronzwaer et al. (2002), the highest rates being reported from Mediterranean countries.

Another important factor in antimicrobial use in the community within the Mediterranean countries concerns self-medication or obtaining these drugs without prescription. Reports describing antibiotic self-medication in the region have originated from Spain (Orero et al. 1997), Greece (Mitsi et al. 2005), and Malta (Borg and Scicluna 2002). A recent study using standardized methods to compare the prevalence of antimicrobial self-medication in 19 European countries reported high rates in eastern and southern Europe where respondents were 6.8 times more likely to self-medicate than respondents in northern and western countries (Grigoryan et al. 2006). The most common reasons for self-medication were upper respiratory tract infections, normally viral in etiology. Over-the-counter dispensing in pharmacies and use of stocks from past prescriptions were identified as the two most common sources of self-medication. Such practices are by no means limited to nationals of the Mediterranean countries concerned. Vaananen and colleagues (2006) found that 41% of Finnish expatriates living permanently in southern Spain and who had used antibiotics in the 6 months prior to the study, had obtained them without a medical prescription. Such a finding in a population not accustomed to such practices would indicate significant underlying sociocultural factors which have not been sufficiently investigated. Very little data are available on use of antibiotics in ambulatory care within the southeastern Mediterranean countries. Not all countries mandate the need for a prescription for an antibiotic to be dispensed. Even where this is required, anecdotal evidence seems to suggest that in this region self-medication is at least as common.

Information on use of antibiotics in hospital care is also incomplete. Nevertheless, preliminary data from the pan-European study entitled "Development of Strategies for Control and Prevention of Antibiotic Resistance in European Hospitals" (ARPAC) would support a scenario of more intensive regional antimicrobial use. Reports at the ARPAC Consensus Conference [www.abdn.ac.uk/arpac] indicated that participating hospitals in the south of Europe reported a median consumption of 82 DDD/100 bed days, which was significantly higher than for all other regions of Europe. Furthermore, a substantial proportion of these drugs

were composed of wide spectrum combinations of penicillins with β-lactamase inhibitors. Use of these antimicrobials, particularly co-amoxiclav, has been linked through multivariate analysis with nosocomial MRSA incidence (Crowcroft et al. 1999). Mediterranean hospitals in the study also had the highest use of non-penicillin β-lactams, 60% being carbapenems and third- or fourth-generation cephalosporins; these antimicrobial groups are also recognized as critical factors for development of resistance. Very little information is currently available about the use of antibiotics in the south and east of the region. One important challenge facing some of these hospitals is the impact and reliance on donations of antibiotics by pharmaceutical companies or voluntary organizations. This may result in skewed decision making in which an antimicrobial is prescribed not because it is the most appropriate but as a result of it being the easiest available.

## *Antibiotic Policy Development*

Throughout the region there is considerable variation in national schemes to encourage better antibiotic stewardship although it is apparent that, faced with the ever-increasing problem of antimicrobial resistance, many countries are setting up national entities to coordinate these activities. A recent consultation exercise by the European Commission indicated that all Mediterranean EU member countries either had such an infrastructure in place or were in the process of developing it (European Commission 2005). Where established, initiatives tend to concentrate primarily on surveillance of resistance epidemiology and feedback of data to prescribers. These seem to be reasonably developed in the European part of the Mediterranean, although substantial room for improvement still exists. On the other hand, ARMed data for the south and east of the Mediterranean indicate that national antimicrobial coordination is quite limited, especially in the middle-eastern countries (Borg et al. 2005).

Initiatives for better antibiotic use do not necessarily follow on from those of antimicrobial resistance surveillance as shown by several European countries in the region having a long track record of antimicrobial resistance surveillance yet possessing a less well-established infrastructure where antibiotic consumption is concerned. Moro et al. (2003) identified various lacunae in antibiotic policy development in Italian hospitals. While a formulary was present in almost 90% of hospitals, a functional therapeutics committee was reported by half of respondents. Only 18% of hospitals had a specific antibiotic subcommittee which had met at least once a year. Data on antibiotic consumption in Defined Daily Dosage was available in 12%, with written protocols for antimicrobial prophylaxis in surgery found in 37% of hospitals. The authors also identified differences in policy availability depending on the size of the hospital in question. Drugs and Therapeutics committees, antimicrobial surgical prophylaxis policies, and surveillance of antibiotic consumption were infrequently present in hospitals with less than 150 beds (28, 20, and 4.6%, respectively) whereas they were found at significantly higher frequencies in hospitals having more than 500 beds (74, 46, and 15%, respectively).

Feedback from ARMed indicates that in the southeastern Mediterranean, antibiotic policy development and prescriber feedback of resistance epidemiology is often lacking. Even where these initiatives are in place, sociocultural elements may pose considerable obstacles to progress. Interventions which have been long accepted in Western countries, including prescriber audit and antibiotic restriction, may be difficult to implement especially among senior physicians who possess a high level of influence at both healthcare institution and even national level. Educational opportunities may well be limited and the influence of pharmaceutical companies on prescribing decision making is often significant. Donations of considerable quantities of antibiotics to healthcare institutions are common practices which often introduce a prescribing bias since the choice of drug would be influenced not on what is microbiologically indicated but rather on what is easily available. Misconceptions may be present among prescribers who feel that individual experience is more relevant than evidence-based recommendations. These attitudes, however, are not restricted to this part of the Mediterranean and are reported in other parts of the region.

Italian doctors interviewed by Formoso et al. (2001) perceived clinical practice guidelines as less useful than personal knowledge and information garnered from conferences, colleagues, and textbooks. The majority of respondents felt that practice guidelines were developed mainly for cost-containment reasons and were concerned that they were not applicable to individual patients and local settings. They also expressed disagreement with multidisciplinary approaches that involved health professionals other than physicians. Primary care physicians tended to show the greatest resistance toward guideline development. It is clear that such attitudes, which seem to concord with informal feedback and experience from other Mediterranean countries, are a major obstacle toward improved dissemination of evidence based protocols and practice in the whole region.The causal link between antibiotic resistance and consumption has been well established (McGowan 1983). Monnet (2000) has proposed, through mathematical modeling, that in environments where there is both a high prevalence of resistance as well as evidence of heavy antibiotic consumption, the area of improvement that is likely to have the biggest impact on resistance is control of antibiotic use. Such improvement can be obtained through antibiotic stewardship programs that aim to ensure that the use of antibiotics is commensurate to the clinical circumstances and the local resistance epidemiology (Paterson 2006). To this end, feedback to prescribers of local antimicrobial resistance information as well as development and dissemination of antibiotic prescribing guidelines based on the local circumstances should have a major impact in combating the documented high prevalence of antimicrobial resistance in the region. In addition, improved audit and accreditation of hospitals, currently lacking in the whole region, should also improve the consistency of adoption of such programs.

## Prevention and Control of Multiresistant Infections

Equally relevant to the epidemiology of antibiotic resistance, particularly in hospitals, are the initiatives taken at national and individual hospital level to prevent spread of multiresistant organisms within healthcare institutions. Active infection control programs are also inconsistently present in hospitals of the region. Whereas infection control is a national requirement in almost all European countries, the same does not apply in the rest of the region (Table 9.1). Borg et al. (2005) report inconsistency in their establishment within hospitals in the south and east where, if present, programs for infection control were often implemented mainly in larger teaching hospitals. In most countries there were no national requirements for the employment of infection control doctors and nurses in hospitals, particularly in North Africa where such designated professionals are normally only found in specialist centers. Despite the high prevalence of multi-drug-resistant organisms within the region, only a few countries have official entities responsible for the control of antibiotic resistant organisms, surveillance of nosocomial infections, and audit of hospital infection control activities. National differences have also been identified in the implementation of infection control training. The emphasis on HAI training is sporadic and specific infection control lectures were only sparsely included at the undergraduate level or not at all.

This variance is not surprising as the non-European Mediterranean countries are, to a varying extent, also still developing their socioeconomic, educational, and healthcare infrastructures to reach levels comparable to those of their Western counterparts. In developing countries, substantial deficiencies in healthcare quality and delivery are often due to insufficient budgets, low salaries for health personnel, and diversion of resources to areas of "higher priority" or to produce more tangible investments (Meers 1998). Nevertheless, it would be difficult to explain the lack of IC initiatives based solely on these premises, as even in the more affluent European countries bordering the northern Mediterranean shores, implementation of IC programs has also been shown to be less than comprehensive. Moro and colleagues (2003) also showed that just 1.6% of surveyed Italian hospitals had a policy for the control of MRSA infections. Inadequate resources and lack of trained personnel were cited as being obstacles to optimal infection control intervention in reports from Greece and Spain (Gikas et al. 2004, Rodriguez-Baño and Pascual 2001). Brusaferro and colleagues (2003) found that only 3% of hospitals in southern Italy had an active IC program, as compared to 30% in the northern regions of the same country. These reports would therefore suggest that emphasis on nosocomial infections and their control requires enhancement within the whole Mediterranean region.

However, in order for improvement to be achieved, further developments are clearly needed at the individual hospital level. It is promising that many Mediterranean hospitals have established Infection Control Committees to coordinate infection control initiatives and training within their particular healthcare institutions. Infection control teams composed of designated and trained Infection Control Doctors and Nurses are, however, often absent despite

TABLE 9.1. National antimicrobial resistance (AMR) policies or initiatives within Mediterranean countries[a]

| | AMR activities coordination | Surveillance of AMR | Feedback of AMR data | Rational antibiotic use in hospitals | Infection control activities | Mandatory Infection Control Committees in hospitals | Infection Control Nurse (ICN) requirements | Audit / accreditation of hospitals | Undergraduate training & CME actvities in HIC |
|---|---|---|---|---|---|---|---|---|---|
| Cyprus | D[b] | N | N | N | Y | Y | N | N | Y |
| France | Y | Y | N | Y | Y | Y | Y | Y | Y |
| Greece | Y | Y | Y | Y | Y | Y | Y | N | N |
| Italy | D | Y | Y | N | Y | N | N | N | N |
| Malta | Y | Y | Y | Y | Y | N | N | N | N |
| Slovenia | N | N | N | Y | N | Y | N | N | Y |
| Spain | Y | Y | Y | N | Y | Y | N | Y | Y |
| Algeria | Y | Y | Y | Y | Y | Y | N | N | Y |
| Egypt | N | N | N | N | N | N | N | Y | Y |
| Jordan | N | N | N | Y | N | Y | Y | N | N |
| Lebanon | N | N | N | Y | N | Y | Y | N | N |
| Libya | N | N | N | N | N | Y | Y | N | N |
| Morocco | N | Y | N | Y | N | N | N | N | D |
| Syria | N | N | N | N | N | Y | N | N | N |
| Tunisia | Y | Y | Y | N | N | Y | N | N | Y |
| Turkey | N | N | N | Y | N | Y | Y | N | N |

[a] Adapted from Borg et al. (2005) and European Commission (2005).
[b] D: in development; Y: Present; N: absent.

being widely regarded as the cornerstone of an effective IC program (Scheckler et al. 1998). In particular, the critical position of infection control nurse still has some way to go in order to be fully established throughout the region, even in the more economically affluent nations. In fact, only two of the northern European countries indicated that this position is a national requirement for healthcare institutions, although in many cases such professionals are to be found in larger hospitals (Table 9.1). This constitutes a potential drawback that could surely hamper IC outcomes. ARMed results indicate a low frequency of Mediterranean institutions having infection control guidelines available for hospital staff to consult and comply with. This is undoubtedly yet another major obstacle to progress. A recent study on the worldwide variation of MRSA control identified that southern Mediterranean participants were reasonably at par with other healthcare facilities in surveillance programs, but significantly inferior in adoption of standard isolation precautions at ward level, particularly use of gloves, gowns, hand hygiene, and isolation facilities (Richet et al. 2003). It is all very well for Infection Control Committees to be set up within hospitals, but these require an effector mechanism to produce the most appropriate recommendations and to ensure that clinical staff "own" these and put them into practice. This has been reported to be particularly applicable to developing countries where nurses, doctors, and patients are often unaware of the importance of infection control and its relevance to safe healthcare (Sobayo 1991).

## Conclusion

Past observations have noted that healthcare delivery in the Mediterranean countries often gives greater emphasis to cure rather than prevention (Taker 1997). This could explain the general lack of policy development and establishment for both antibiotic use as well as prevention and control of nosocomial infections. Targeted interventions have been shown to be possible and cost-effective even in limited resource settings (Calalcante et al. 1989), particularly when traditional interventions are adapted for local circumstances (de Gentile et al. 2001). A strong argument can be made, as elsewhere, that a program for surveillance of antimicrobial resistance, encouragement of better antibiotic prescribing, and prevention of nosocomial infections within this region, quite apart from paying for itself would also generate other direct and indirect benefits to patients and, indeed, the whole of society.

*Acknowledgments:* The assistance of Dr. Jos Monen and the management team of the European Antimicrobial Resistance Surveillance System (EARSS) in compiling Figures 9.1–9.5 is gratefully acknowledged.

## *References*

Antibiotic Resistance and Control in the Mediterranean Region (ARMed) (cited 27 May 2006) Available at http://www.slh.gov.mt/armed

ARPAC Consensus Conference (cited 27 May 2006) Available at http://www.abdn.ac.uk/arpac

Borg MA, Scicluna EA (2002) Over-the-counter acquisition of antimicrobial drugs in the Maltese general population. Int J Antimicrob Agents 20:253–7.

Borg MA, Cookson BD, Scicluna EA, ARMed Project Steering Group and Collaborators (2005) National infection control initiatives within countries of the southern and eastern Mediterranean. J Hosp Infect 60:182–5.

Borg M, Scicluna E, De Kraker M, et al (2006) Antibiotic resistance in the southeastern Mediterranean—Preliminary results from the ARMed project. Eur Surveill 11:164–7

Bouchillon SK, Johnson BM, Hoban DJ, et al (2004) Determining incidence of extended spectrum beta-lactamase producing Enterobacteriaceae, vancomycin-resistant Enterococcus faecium and methicillin-resistant *Staphylococcus aureus* in 38 centers from 17 countries: The PEARLS study 2001–2002. Int J Antimicrob Agents 24:119–24.

Bronzwaer SLAM (2003) *Streptococcus pneumoniae* susceptibility data in Europe, in Bronzwaer SLAM. European antimicrobial resistance surveillance as part of a Community strategy. Amersfoort, pp 51–76.

Bronzwaer SL, Cars O, Buchholz U, et al (2002) A European study on the relationship between antimicrobial use and antimicrobial resistance. Emerg Infect Dis 8:278–82.

Brusaferro S, Quattrin R, Barbone F, et al (2003) Factors influencing hospital infection control policies in Italian hospitals. J Hosp Infect 53:268–73.

Calalcante MD, Braga OB, Teofilo CH, et al (1991) Cost improvements through the establishment of prudent infection control practices in a Brazilian general hospital, 1986–1989. Infect Control Hosp Epidemiol 12:649–53.

Central Intelligence Agency. World Fact Book (cited 27 May 2006) Available at http://www.cia.gov/cia/publications/factbook/index.html

Crowcroft NS, Ronveaux O, Monnet DL, Mertens R (1999) Methicillin-resistant Staphylococcus aureus and antimicrobial use in Belgian hospitals. Infect Control Hosp Epidemiol 20:31–6.

de Gentile A, Rivas N, Sinkowitz-Cochran RL, et al (2001) Nosocomial infections in a children's hospital in Argentina: Impact of a unique infection control intervention program. Infect Control Hosp Epidemiol 22:722–66.

European Antimicrobial Resistance Surveillance System. EARSS Annual Report 2004 (cited 27 May 2006) Available at http://www.rivm.nl/earss

El Kholy A, Baseem H, Hall GS, et al (2003) Antimicrobial resistance in Cairo, Egypt 1999–2000: A survey of five hospitals. J Antimicrob Chemother 51: 625–30.

European Commission (2005) Detailed analysis of Member States' reports on the implementation of the Council recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine (cited 27 May 2006) Available at http://europa.eu.int/eurlex/lex/LexUriServ/site/en/com/2005/com2005_0684en01.pdf

Felmingham D, Grüneberg RN, and the Alexander Project Group (1996) A multicentre collaborative study of the antimicrobial susceptibility of community-acquired lower respiratory tract pathogens 1992–1993. J Antimicrob Chemother 30 (Suppl A): 1–57.

Fluit AC, Jones ME, Schmitz FJ, et al (2000) Antimicrobial resistance among urinary tract infection (UTI) isolates in Europe: Results from the SENTRY Antimicrobial Surveillance Program 1997. Antonie Van Leeuwenhoek 77:147–52.

Formoso G, Liberati A, Magrini N (2001) Practice guidelines: Useful and "participative" method? Survey of Italian physicians by professional setting. Arch Intern Med 161:2037–42.

Gikas A, Roumbelaki M, Pediaditis J, et al (2004) Prevalence of nosocomial infections after surgery in Greek hospitals: Results of two nationwide surveys. Infect Control Hosp Epidemiol 25:319–24.

Goossens H, Ferech M, Vander Stichele R, et al (2005) Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. Lancet 365:579–87.

Grigoryan L, Haaijer-Rysjamp FM, Burgerhof JG, et al (2006) Self-medication with antimicrobial drugs in Europe. Emerg Infect Dis 12:452–9.

Gür D, Unal S (2001) Resistance to antimicrobial agents in Mediterranean countries. Int J Antimicrob Agents 17: 21–6.

Jones RN, Pfaller MA, the MYSTIC Study Group (Europe) (2003) Antimicrobial activity against strains of Escherichia coli and Klebsiella spp. with resistance phenotypes consistent with an extended-spectrum beta-lactamase in Europe. Clin Microbiol Infect 9:708–12.

McGowan JE Jr (1983) Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis 5:1033–48.

Meers PD (1988) Infection control in developing countries. J Hosp Infect 11:406–10.

Mitsi G, Jelastopulu E, Basiaris H, Skoutelis A, Gogos C (2005) Patterns of antibiotic use among adults and parents in the community: A questionnaire-based survey in a Greek urban population. Int J Antimicrob Agents 25:439–43.

Monnet DL (2000) Toward multinational antimicrobial resistance surveillance systems in Europe. Int J Antimicrob Agents 15:91–101.

Moro ML, Petrosillo N, Gandin C (2003) Antibiotic policies in Italian hospitals: Still a lot to achieve. Microb Drug Resist 9:219–22.

Orero A, Gonzales J, Prieto J (1997) Antibiotics in Spanish households. Medical and socioeconomic implications. URANO Study Group [article in Spanish]. Med Clin (Barc) 109:782–5.

Paterson DL (2006) The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. Clin Infect Dis 42:S90–5.

Richet HM, Benbachir M, Brown DFJ, et al (2003) Are there regional variations in the diagnosis, surveillance and control of methicillin-resistant *Staphylococcus aureus*? Infect Control Hosp Epidemiol 24: 334–41.

Rodriguez-Baño J, Pascual A (2001) Hospital infection control in Spain. J Hosp Infect 48:258–60.

Scheckler WE, Brimhall D, Buck AS, et al (1998) Requirements for infrastructure and activities of infection control and epidemiology in hospitals: A consensus report. Infect Control Hosp Epidemiol 19:91–3.

Schito GC, Debbia EA, Marchese A (2000) The evolving threat of antibiotic resistance in Europe: New data from the Alexander Project. J Antimicrob Chemother 46 Suppl T1:3–9.

Sobayo EI (1991) Nursing aspects of infection control in developing countries. J Hosp Infect 18:388–91.

Taker AR (1997) Report on an Expert Meeting on Health and Social Welfare in the Euro-Mediterranean region. European Commission. The Hague, 1–46.

Vaananen MH, Pietila K, Airaksinen M (2006) Self-medication with antibiotics—Does it really happen in Europe? Health Policy 77: 166–71.

# Chapter 10
# Cystic Fibrosis—Coping with Resistance

Oana Ciofu and Niels Høiby

## Cystic Fibrosis: Chronic Lung Infection with *P. aeruginosa*

Reduced volume of the epithelial lining fluid and viscous mucus leading to dysfunction of the mucociliary escalator are the consequences of a nonfunctional CFTR chloride channel in the lungs of patients with cystic fibrosis (CF). This impairment of the noninflammatory defense mechanism of the respiratory tract leads to early recruitment of the inflammatory defense mechanism, e.g., polymorphonuclear leukocytes (PMN) and antibodies. As a consequence, the patients suffer from recurrent and chronic respiratory tract infections caused mainly by bacteria such as *S. aureus, H. influenzae, B. cepacia*, and especially *P. aeruginosa*. The treatment of *P. aeruginosa* lung infection which is the main cause of morbidity and mortality in these patients includes beta-lactam antibiotics, aminoglycosides, fluoroquinolones, and polymyxins.

Aggressive antimicrobial treatment of chronic *P. aeruginosa* infections in the CF lung improves lung function and life expectancy but the infection is rarely if ever eradicated. The main reason is most likely the biofilm mode of growth, but the frequent occurrence of multiply drug resistant (MDR) *P. aeruginosa* in CF patients implies that conventional resistance mechanisms also play a role.

The genetic basis for MDR *P. aeruginosa* is often due to simultaneous mutations in a single bacterial cell of several genes causing antibiotic resistance. Thus, one bacterial cell might produce enzymes that degrade antibiotics, have antibiotic targets of low affinity, and overexpress efflux pumps which have a broad spectrum of substrates. Each of the necessary mutations arises in one cell per $10^7$ to $10^9$. Achievement of multiple mutations in a bacterial population size of $10^8$–$10^{10}$/ml sputum as is attained under infection of the CF lung (Høiby et al. 2001) implies the presence of a hypermutable bacterial subpopulation and the presence of high percentages of hypermutable *P. aeruginosa* isolates has been found in CF patients (Oliver et al. 2000, Ciofu et al. 2005). Acquisition of hypermutability confers an advantage to the bacteria in the stressful and fluctuating environment of the CF lung where they have to face challenges imposed by the host immune system as well as to cope with high doses of various antibiotics administered repeatedly for prolonged periods of time (LeClerc et al. 1996). It is important to notice that stable

hypermutability does not confer advantage by itself due to the high number of deleterious mutations but the association (hitchhiking) with rare favorable mutations confers a survival advantage (Radman et al. 2000).

The hypermutable phenotype of CF *P. aeruginosa* isolates is due to alterations in the DNA error repair systems: MMR (mismatch repair system) or GO (DNA oxidative lesions repair system) (Oliver et al. 2000). The mismatch repair genes present in *P. aeruginosa* are *mutS, mutL*, and *uvrD* and the DNA oxidative repair genes are *mutT, mutY*, and *mutM*.

There are two main conditions that together with the antibiotic selective pressure might predispose to bacterial hypermutability in the CF lung: the biofilm mode of growth and the oxidative stress caused by the PMN dominated lung inflammation.

Increased mutation rates have been found in stationary-phase, nondividing cells (Alonso et al. 1999). A large bacterial subpopulation in biofilms is in stationary phase as judged from the transcriptome analysis of the bacterial gene expression at different stages of biofilm formation (Hentzer et al. 2005). These mutational events are the basis of the so-called adaptive resistance (or stress-induced mutagenesis) and the stress-enhanced bacterial mutation is transient. It has been proposed that the mutation rate under stress increases from $10^{-8}$–$10^{-9}$ to $10^{-2}$–$10^{-3}$ (Alonso et al. 1999) so that bacteria carrying mutations in several genes could emerge in population sizes attainable during infection. Taddei et al. (1997) suggested the benefit of transient mutator status by generation of beneficial mutations in the rapid adaptive phase, followed by the reversion of the mutator allele to create more stable nonmutator hosts that nevertheless retain the advantageous mutations arising in the rapid period. Thus, under long-term antibiotic therapy the biofilm mode of growth accelerates the development of conventional resistance mechanisms due to selection of antibiotic-resistant mutants in a transient hypermutable bacterial population.

Besides the transient increase in mutation rates that occurs in biofilm, stable hypermutable bacterial pathogens (mutators) with MDR phenotype are isolated more frequently from patients with CF as compared to other groups of patients (Oliver et al. 2000).

An association between occurrence of mutators and the inflammatory response in the CF lung has been found (Ciofu et al. 2005). The basis for this hypermutability might be the increased DNA oxidative damage caused by the highly mutagenic reactive-oxygen species (ROS) liberated by activated PMNs which dominate the chronic inflammation in CF (Ciofu et al. 2005).

Thus, both the biofilm mode of growth which causes transient hypermutability and the oxidative stress due to inflammation in the CF lung which create conditions for stable hypermutability contribute to an environment where *P. aeruginosa* acquires high mutation rates. Therefore, occurrence with increased frequency of mutations in genes leading to antibiotic resistance and selection of these resistant mutants by long-life antibiotic treatment is the basis for the high rate of MDR *P. aeruginosa* from CF patients. Besides the mutational resistance, adaptive resistance to antibiotics like aminoglycosides and polymyxins also occurs in nondividing cells in biofilm. Adaptive resistance is the phenomenon by which a population of

initially susceptible bacteria acquires transient resistance to the antibiotic that is subsequently lost during growth in the absence of the antibiotic.

Coping with antibiotic resistance in CF pathogens is, therefore, a rather complicated issue and implies (1) coping with the conventional resistance mechanisms, (2) coping with biofilm-related resistance mechanisms, and (3) coping with hypermutability and oxidative stress in the CF lung.

## Conventional Mechanisms of Resistance

### *Resistance to β-Lactam Antibiotics*

The overproduction of chromosomally encoded AmpC cephalosporinase is considered the main mechanism of resistance of *P. aeruginosa* CF isolates to β-lactam antibiotics (Sanders et al. 1988, Giwercman et al. 1990). Secondary plasmid-encoded β-lactamases have rarely been reported in CF strains. However, as more and more metallo-β-lactamases with carbapenemase activity have been described in the past few years in *P. aeruginosa* isolates in several parts of Europe and Asia, one has to be aware of the risk that such secondary β-lactamases might spread to *P. aeruginosa*, infecting CF patients (Walsh et al. 2005).

The most common phenotype of β-lactamase production in CF isolates is the partially derepressed phenotype with high basal levels of β-lactamase that can be induced further to higher levels in the presence of β-lactam antibiotics (Ciofu 2003). The role of this β-lactamase phenotype is important especially for the resistance to β-lactam antibiotics acting as strong inducers (carbapenems like imipenem). However, not all β-lactams are strong inducers and the overexpression of the MexAB-OprM efflux pumps might play, together with β-lactamases, an important role in the resistance to poor inducers (e.g., piperacillin). Accordingly, it has been observed that a proportion of CF isolates have a nonfunctional MexAB-Opr Mpump suggesting that this latter system does not play a major role in the resistance of *P. aeruginosa* to β-lactams in the CF context (Patrick Plésiat personal communication). Totally derepressed β-lactamase production is encountered in some clinical CF isolates (4 out of 162 CF isolates) (Ciofu 2003) and is responsible for the resistance to both poor and strong inducer β-lactam antibiotics, independent of the overexpression of efflux pumps (Nakae et al. 1999). We have found an insertion sequence (IS 1669) inactivating the *ampD* gene in several resistant clinical *P. aeruginosa* isolates with constitutive high expression of chromosomal β-lactamase. The β-lactamase phenotype reversed to basal levels after complementation with wild-type *ampD* (Bagge et al. 2002).

### *Resistance to Fluoroquinolones*

Fluoroquinolones are an important group of antibiotics for the oral treatment of *P. aeruginosa* infection in the CF lung and in the Copenhagen CF Center ciprofloxacin has routinely been used since 1987 together with colistin inhalations

for the early aggressive treatment of *P. aeruginosa*. This therapeutic strategy prevents chronic *P. aeruginosa* infection in 80% of the patients in the treated group compared to untreated controls (Valerius et al. 1991) and changed the epidemiology of the infection, with fewer young patients becoming chronically infected (Frederiksen et al. 1999). This early, aggressive eradication therapy has not led to resistance problems (Høiby et al. 2005). When, however, ciprofloxacin was used to treat chronic *P. aeruginosa* infection, resistance developed (Ciofu 2003). Increased resistance to ciprofloxacin (MIC $\geq$2 mg/L) was found in CF *P. aeruginosa* isolates from chronically infected patients and the mechanism of resistance was expression of two efflux systems (MexCD-OprJ and MexEF-OprN) and simultaneous mutations in the target gene coding for the DNA gyrase. Overexpression of efflux systems seems to be a characteristic of CF isolates but was not found in fluoroquinolone-resistant *P. aeruginosa* isolates from urinary tract infection whose resistance mechanisms were mutations in the target genes DNA topoisomerase IV and gyrase (Jalal et al. 2000).

## *Resistance to Aminoglycosides*

Tobramycin is a drug frequently used for monotherapy or in combination with β-lactam antibiotics for the IV courses against chronic *P. aeruginosa* infection. In the last 15 years inhalations with tobramycin have also been used and have proved to be safe and efficient treatment of chronic *P. aeruginosa* lung infection (Ramsey et al. 1999). Inhalations with tobramycin were introduced in 1994 in the treatment of Danish CF patients and tobramycin resistant *P. aeruginosa* strains have been occasionally isolated (Ciofu 2003). Both adaptive and mutational resistance have been described for aminoglycosides. *In vivo*, the adaptive resistance of *P. aeruginosa* to aminoglycosides is probably playing an important role in the efficacy of the treatment with tobramycin of CF patients (Barclay et al. 1996). It has been demonstrated that adaptive resistance is associated with decreased accumulation of aminoglycosides in the bacterial cell (Karlowsky et al. 1996). Aminoglycoside-resistant clinical isolates, particularly from CF patients, have been characterized by impermeability and no isolates were found to contain aminoglycoside hydrolyzing enzymes (MacLeod et al. 2000).

The reduced level of aminoglycoside accumulation that characterizes both impermeability and adaptive resistance has been explained in recent studies by the involvement of MexXY-OprM efflux system whose overexpression is due to mutation in the negative regulator gene *mexZ* (Vogne et al. 2004). In the CF lung, stable and transient derepression of MexXY allows *P. aeruginosa* to with stand the high selective pressure exerted by repeated systemic or aerosolized administration of aminoglycosides such as tobramycin (Patrick Plésiat personal communication).

The two-component regulatory system PhoP-PhoQ which responds to divalent ion concentration is involved in the susceptibility of *P. aeruginosa* to both aminoglycosides and polymyxins (Macfarlane et al. 2000). The details of PhoPQ involvement in aminoglycoside resistance remain to be fully elucidated but its involvement in resistance to polycations and to aminoglycosides appear to differ.

It is possible that PhoPQ-dependent aminoglycoside resistance in *P. aeruginosa* may involve modification of the lipid A portion of LPS. Changes in the LPS component of the outer membrane have long been implicated in resistance to aminoglycoside in clinical isolates (Shearer and Legakis 1985, Katsorchis et al. 1985). This is not surprising given that LPS appears to be a necessary target for aminoglycoside binding in the process of its uptake across the outer membrane of *P. aeruginosa* (Hancock et al. 1981). The impermeability resistance is typically low-to moderate-level panaminoglycoside resistance. High-level panaminoglycoside-resistant strains were shown to carry a gene, *rmtA*, that encodes a 16 S rRNA methylase on mobile genetic elements (Yamane et al. 2004).

## *Resistance to Polymyxins*

In the Copenhagen CF Center, colistin has been routinely used since 1987 in the early aggressive treatment as combination of inhaled colistin and oral ciprofloxacin and also for the maintenance therapy of chronic *P. aeruginosa* infection (Jensen et al. 1987). The early aggressive eradication therapy does not result in resistance problems (Høiby et al. 2005) in contrast to maintenance therapy of chronic *P. aeruginosa* infection, where resistance to both colistin and ciprofloxacin occurs (Johansen et al. 2003). Both adaptive and mutational resistance have been described for polymyxins and involve the PhoP–PhoQ two-component system because of its role in promoting an aminoarabinose modification of the lipid A portion of LPS (Moskowitz et al. 2000). Another two-component regulatory system that regulates resistance to polymyxin B and to cationic peptides is the PmrA-PmrB two-component system which is $Mg^{2+}$ regulated and which can be induced by polymyxin B and might be responsible for adaptive resistance (McPhee et al. 2003).

## *Nonmucoid Isolates Are More Resistant Than Mucoid Isolates in Planktonic Growth*

Both mucoid and nonmucoid phenotypes of *P. aeruginosa* with differences in the antimicrobial susceptibility pattern are regularly isolated simultaneously from patients with CF and chronic lung infection. We found that the nonmucoid isolates had significantly higher MIC of several antipseudomonal drugs compared to the mucoid paired isolates and this was in accordance with previous studies (Thomassen et al. 1979, Ballestero et al. 1993, Shawar et al. 1999). Compared to mucoid isolates, higher β-lactamase levels were found in the nonmucoid isolates and this correlated with differences in resistance to β-lactam antibiotics (Ciofu et al. 2001). Alginate is an oxygen scavenger and protects *P. aeruginosa* against phagocytosis and clearance from the lung, so that the mucoid phenotype is better protected than the nonmucoid phenotype against the inflammatory defense mechanisms of the host. Higher levels of DNA oxidative damage (8-oxo-dG) and higher mutation frequencies to rifampicin and streptomycin have been found in nonmucoid isolates compared to paired mucoid isolates from 70 patients with

CF (Ciofu unpublished results). These data suggest that the nonmucoid isolates have an increased potential of acquiring mutations leading to antibiotic resistance than the mucoid isolates. However, several pieces of evidence are available indicating that the pathogenesis of chronic lung infection is related to the mucoid phenotype and that occurrence of mucoid isolates is associated with poor prognosis (Pedersen et al. 1992). This means that antipseudomonal treatment should be primarily directed against the mucoid isolates.

## Biofilm Mode of Growth and Antibiotic Resistance Mechanisms

It is widely recognized that, due to the biofilm mode of growth, bacteria established in biofilms are up to 1000 times more resistant to antimicrobial therapy than their isogenic counterparts cultured as planktonic cells (Nickel et al. 1985, Anwar and Costerton 1990). As bacterial cells that survived the antibiotic treatment of biofilms are often susceptible to antibiotics during planktonic growth, the resistance to antibiotics of biofilms is often referred to as tolerance and these terms will be used as interchangeable in this review. Antibiotic tolerance is defined as the ability of bacteria to survive but not grow in the presence of antibiotic concentrations above their MIC.

It is generally accepted now that the biofilm antibiotic tolerance is multifactorial, and only a combination of different mechanisms could account for the levels of resistance observed in biofilms.

Several hypotheses for the high level of resistance of biofilms to antibiotics have been proposed. (1) Reduction of antibiotic penetration: the exopolysaccharide matrix may act as a barrier to antibiotics, slowing the diffusion of antibiotics through the biofilm matrix. (2) The biofilm may cause an altered microenvironment in the individual cells with a low physiological activity of the bacterial cells deep below the surface of the biofilm where anaerobic conditions exist while at the surface of the biofilm, nutrients and oxygen are readily available and the cells grow actively. (3) Bacteria in biofilms can turn on stress-response genes and switch to more tolerant phenotypes upon environmental stresses and the presence of phenotypic variants or persisters cells (Fux et al. 2005). Genes that are differently expressed in biofilms were found to contribute to the antibiotic tolerance. The gene *pvrR* (phenotypic variant regulator) was found to be involved in conversion of wild-type *P. aeruginosa* into a rough colony variant highly tolerant to antibiotics (Drenkard and Ausubel 2002).

Prolonged starvation induces loss of culturability under standard conditions, whereas the cells remain metabolically active and structurally intact. This reversible "viable but nonculturable state" is considered to be the main reason for the low detection rate of biofilm infections by routine cultures. Adaptation for long-term survival presumably represents an active process because it is lost in knockout mutants for *rpoS* and *ppGpp*, two key components for the adaptation to stationary-phase conditions (Murakami et al. 2005).

## *The Response of P. aeruginosa Biofilms to β-Lactams*

(1) The diffusion barrier plays a role for biofilm resistance of *P. aeruginosa* that overproduce β-lactamase due to the presence in the biofilm matrix of β-lactamases which will hydrolyze the β-lactam antibiotics before reaching the bacterial cells. Giwercman et al. (1991) showed that imipenem and piperacillin were able to induce β-lactamase production in *P. aeruginosa* biofilms.

Nichols et al. (1989) predicted from mathematical models that the biofilm would not afford protection against diffusion of β-lactam antibiotics into the bacteria embedded in the biofilm as long as the level of chromosomal β-lactamase is low. However, bacteria expressing a high level of chromosomal β-lactamase growing in biofilms would be exposed to reduced concentration of β-lactam antibiotics due to accumulation of the enzyme in the polysaccharide matrix. The extracellular β-lactamase would inactivate the antibiotic as it penetrates, thereby protecting the deeper-lying cells. The source of β-lactamase in biofilm was considered to be from a sacrificial layer of bacteria exposed to an antibiotic, with release of defensive enzymes into the extracellular space. We have shown that the source of β-lactamase in biofilm may also be the membrane vesicles (MVs) containing β-lactamase liberated by resistant *P. aeruginosa* bacteria (Ciofu et al. 2000).

We have also shown that strong inducers like imipenem will induce the β-lactamase through all the bacterial layers while poorer inducers like ceftazidime will influence just the superficial layers of the biofilm, probably due to the inactivation of the antibiotic by β-lactamase (Bagge et al. 2004a) (Figure 10.1).

The protective role played by β-lactamase in impairing the penetration of β-lactams in the biofilm can be seen in Figure 10.2. Treatment with ceftazidime of a biofilm formed by a *P. aeruginosa* CF strain with stable derepressed levels of β-lactamase due to an insertion sequence in *ampD* (*P. aeruginosa ampD*$^{-}$) killed very few bacterial cells (dead bacteria in red) (Figure 10.2A). However, addition of aztreonam improved the efficacy of ceftazidime treatment of the biofilm, probably because aztreonam acts as a β-lactamase inhibitor (Giwercman et al. 1992) (Figure 10.2B).

In addition, meropenem, a β-lactamase stable β-lactam showed good efficacy in the treatment of *P. aeruginosa* biofilms (Moskowitz et al. 2004, Hill et al. 2005). Treatment with ceftazidime of a biofilm formed by the same strain expressing basal levels of β-lactamase due to complemention with the wild-type *ampD* (*P. aeruginosa ampD*+) led to eradication of the biofilm (Figure 10.2C).

In conclusion, these data show that β-lactamases play an important role in the resistance of biofilms to β-lactam antibiotics.

(2) The low physiological activity of the bacterial cells deep below the surface of the biofilm where anaerobic conditions exist (Borriello et al. 2004) will decrease the effect of β-lactam antibiotics which are active on growing cells. Tanaka et al. (1999) showed that bactericidal action of β-lactams against *P. aeruginosa* biofilms is significantly affected at slow growth rates.

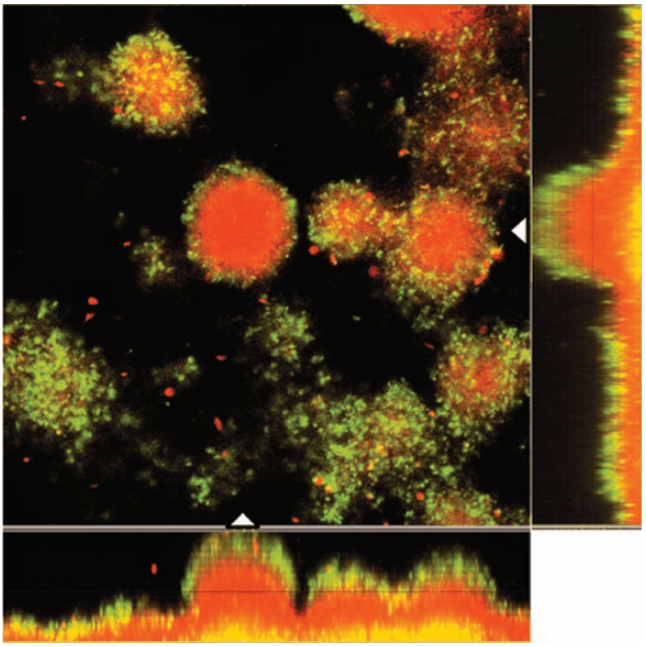


FIGURE 10.1. Induction of β-lactamase in *P. aeruginosa* biofilm. *P. aeruginosa* PAO1 expressing green fluorescent protein (gfp) when the promoter of the AmpC β-lactamase is induced (*PampC-gfp*): 6-day-old biofilm exposed to 100 μg/ml ceftazidime for 4 hours. Detection level of the monitor: 10 μg/ml ceftazidime (Bagge et al. 2004a).

(3) Adaptation of biofilm cells to the stress of β-lactam treatment can be exemplified by the induction of genes involved in alginate production when PAO1 biofilm was treated with sub MIC concentrations of imipenem as seen in Figure 10.3 (Bagge et al. 2004b).

It has recently been reported that cell wall-inhibitory antibiotics, like β-lactams, activate the alginate biosynthesis operon in *P. aeruginosa* (Wood et al. 2006). It has also been shown that the tolerance of biofilm to β-lactams like ceftazidime is quorum-sensing dependent (M. Givskov personal communication).

The adaptation mechanism might involve the RpoS system as it has been shown that RpoS controls the production of extracellular alginate and affects the expression of more than 40% of all quorum-controlled genes identified by transcriptome analysis.

It has been shown in *E. coli* that treatment with β-lactams initiates, via a two-component signal transduction system, an SOS stress response system which stops the cell division and confers protection against the antibiotic (Miller et al. 2004) and such a mechanism has also been described in *P. aeruginosa* (Blázquer et al. 2006).

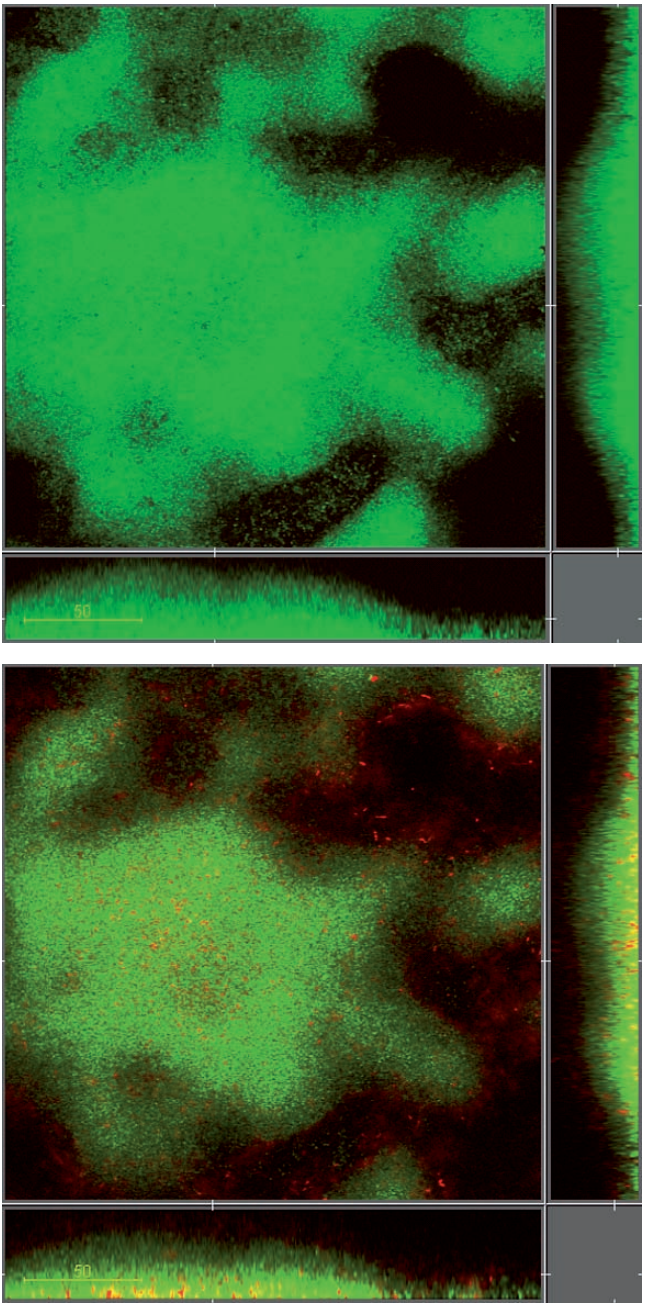



FIGURE 10.2. (A) Treatment of *P. aeruginosa* biofilms with β-lactam antibiotics. *P. aeruginosa ampD*$^{-}$ [levels of AmpC β-lactamase (mU):1050 basal, 4255 induced] expressing green fluorescent protein (gfp) as a tag. A 7 day-old biofilm before (1) and after (2) treatment with ceftazidime (10 times MIC). Propidium iodide was added after day 6 to continuously monitor the killing of the biofilm by ceftazidime during 24 hours. Dead cells are red (Ciofu and Bjarnsholt, unpublished 2005).

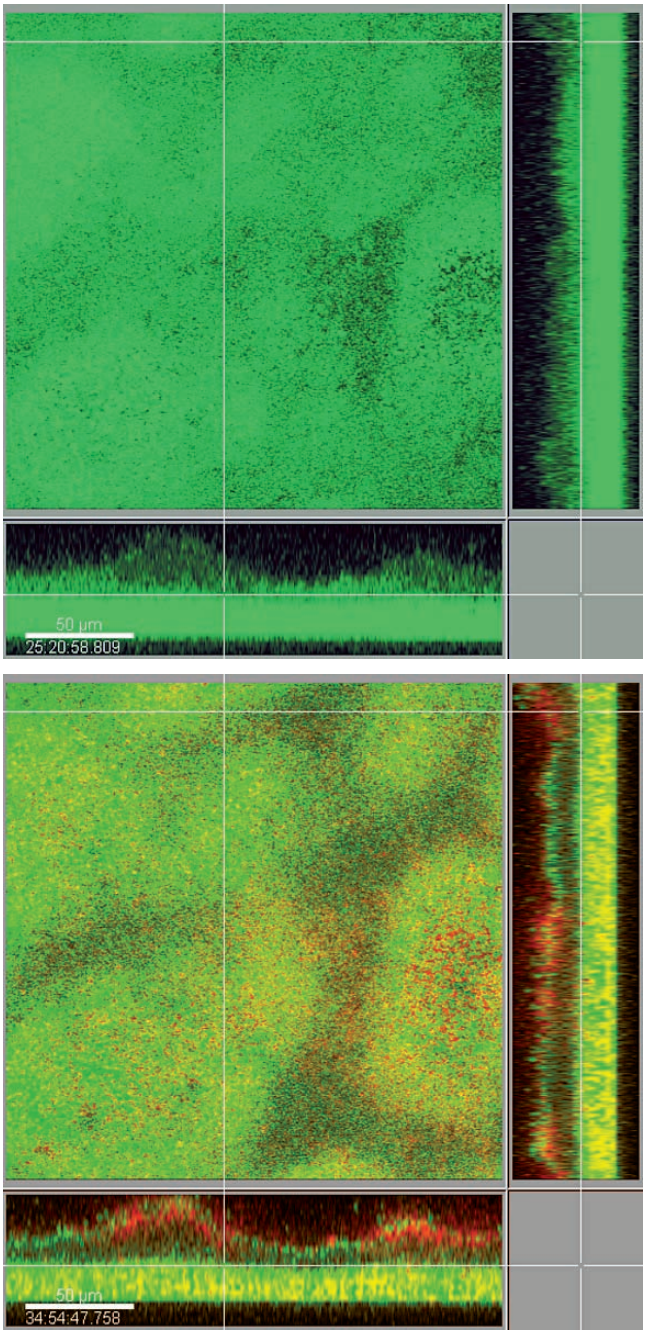



FIGURE 10.2. (B) *P. aeruginosa ampD*$^{-}$. A 7-day-old biofilm before (1) and after (2) treatment with a combination of ceftazidime and aztreonam (10 times MICs). Propidium iodide was added after day 6 to continuously monitor the killing of the biofilm by the combination of ceftazidime with aztreonam during 24 hours. Dead cells are red (Ciofu and Bjarnsholt, unpublished 2005).

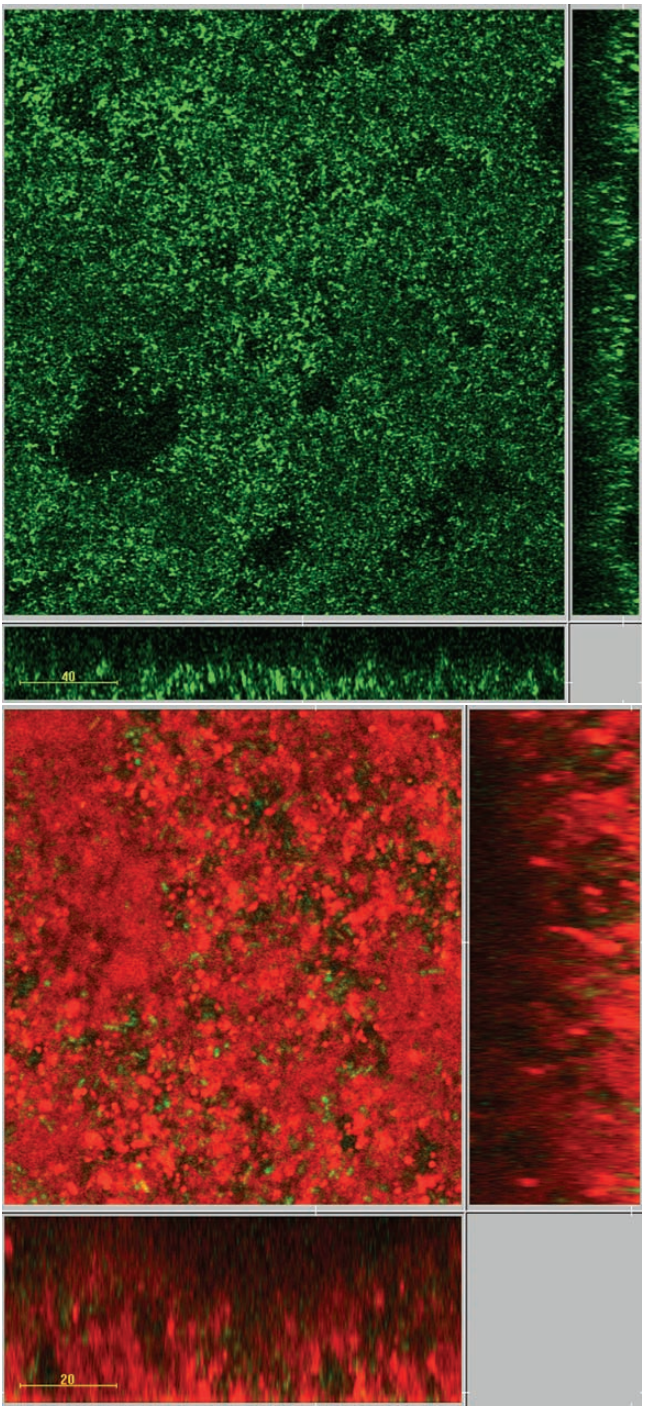



FIGURE 10.2. (C) *P. aeruginosa ampD*$^{+}$ [levels of AmpC β-lactamase (mU): basal 3, induced 175] expressing green fluorescent protein (gfp) as a tag. A 7-day-old biofilm before (1) and after (2) treatment with ceftazidime (10 times MIC). Propidium iodide was added after day 6 to continuously monitor the killing of the biofilm by ceftazidime during 24 hours (Ciofu and Bjarnsholt, unpublished 2005).

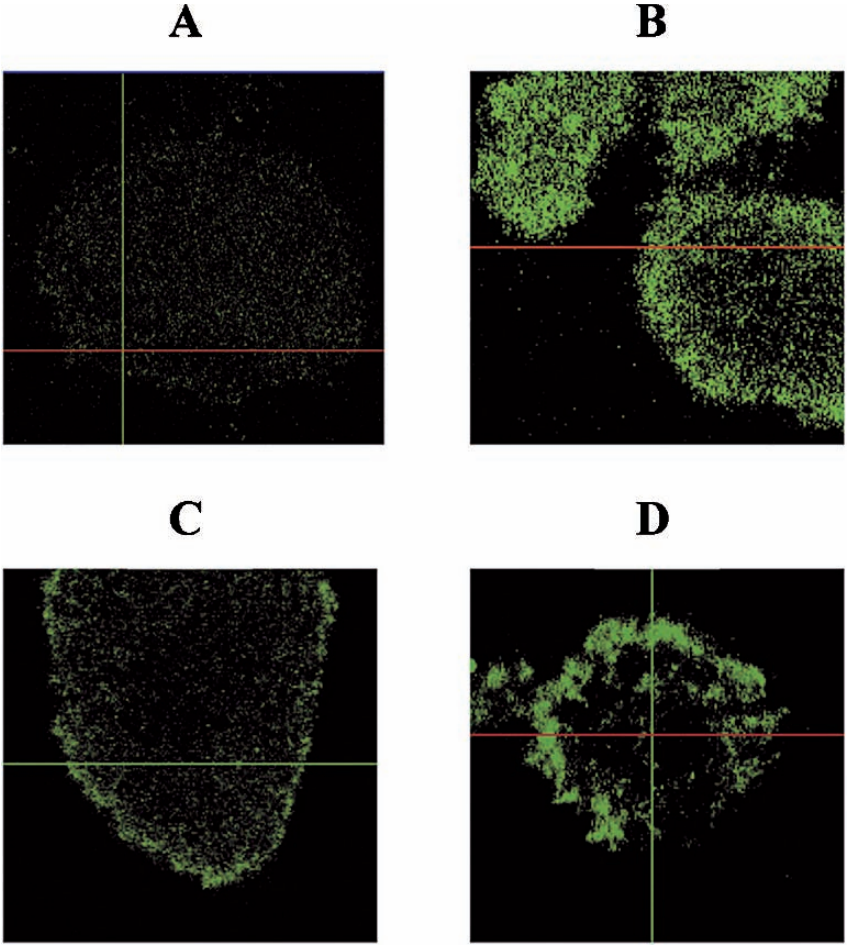



FIGURE 10.3. Induction of alginate in *P. aeruginosa* biofilms treated with sub-MIC concentrations of imipenem. (A) *P. aeruginosa* PAO1 not exposed to antibiotics; (B) PDO300 (a PAO1 derivative constitutively expressing alginate) not exposed to antibiotics; (C) PAO1 exposed to imipenem for 18 hours; (D) PAO1 biofilm exposed to imipenem for 37 hours. Alginate is stained green by ConA-FITC (Bagge et al. 2004b).

## *The Response of P. aeruginosa Biofilms to Fluoroquinolones*

*In vitro*, fluoroquinolones are much more active against bacteria growing in biofilms than β-lactam antibiotics because their mechanism of action is not growth rate dependent (Tanaka et al. 1999). The biofilm inhibitory concentrations (BIC) of quinolones were similar to the conventional MIC in a large collection of *P. aeruginosa* isolates from CF patients (Moskowitz et al. 2004). However, as shown in Figure 10.4 treatment with ciprofloxacin of a *P. aeruginosa* PAO1 biofilm killed only the bacteria located at the surface of the biofilm.

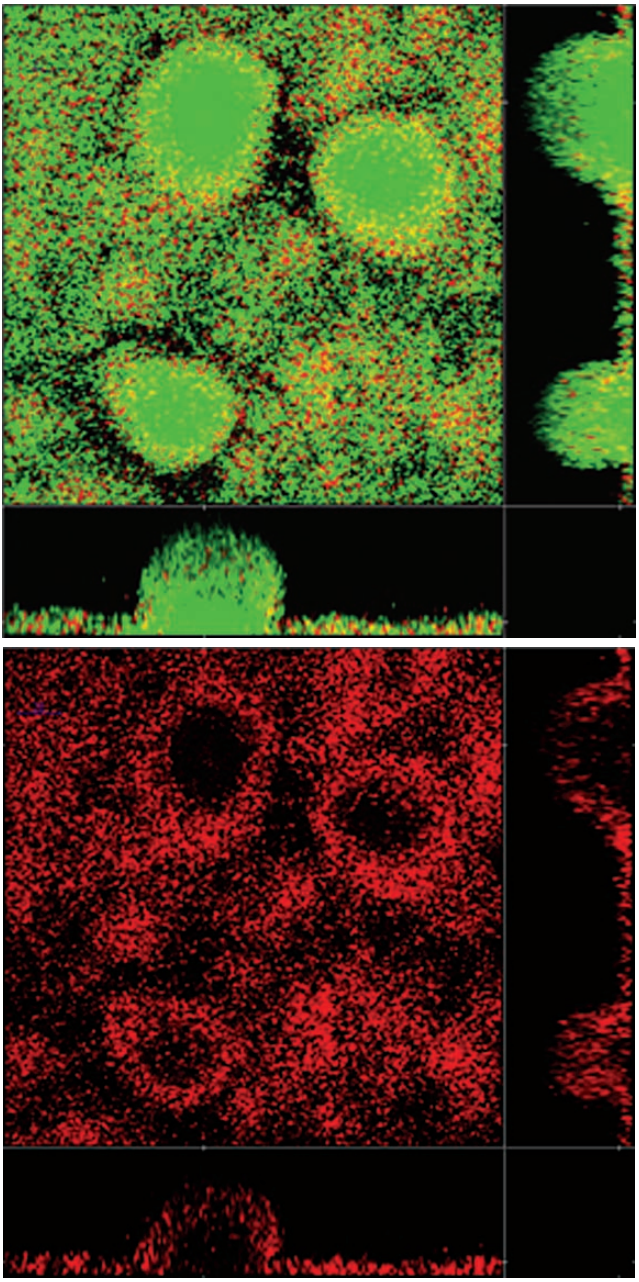


FIGURE 10.4. Treatment of *P. aeruginosa* biofilms with ciprofloxacin. (A) *P. aeruginosa* PAO1 expressing green fluorescent protein (gfp) as a tag was grown as biofilm in a flow chamber for 4 days and was treated for 2 days with ciprofloxacin 10 μg/ml. (B) Propidium iodide was added after day 4 to continuously monitor the killing of the biofilm by ciprofloxacin. Red staining shows that ciprofloxacin kills the bacteria located at the surface of the biofilm. Images are courtesy of Janus Haagensen and Professor Søren Molin, Biocentrum, DTU, Lyngby, Denmark.

Tolerance of biofilms to quinolones does not seem to involve overexpression of efflux pumps (De Kievit et al. 2001). However, it is still possible that induction of these pumps may occur during treatment of biofilms with fluoroquinolones.

The tolerance of biofilms to quinolones seems also to be regulated by quorum-sensing (M. Givskov personal communication).

Quinolone function interferes with DNA replication and it has been shown in *E. coli* that quinolones can be mutagenic (Drlica and Zhao 1997) and induce the SOS system in bacterial cells (Friedberg et al. 1995). These mechanisms might also occur and play a role in the tolerance of *P. aeruginosa* biofilms to fluoroquinolones.

## *The Response of P. aeruginosa Biofilms to Aminoglycosides*

(1) Although it had originally been thought that binding of positively charged antibiotics such as aminoglycosides to the negatively charged exopolysaccharide matrix might play a role in resistance of biofilms to this group of antibiotics (Anwar et al. 1992), more recent studies show that the transport limitation through the exopolysaccharide seems not to be the primary protective mechanism for biofilms exposed to aminoglycosides and ciprofloxacin (Walters et al. 2003)

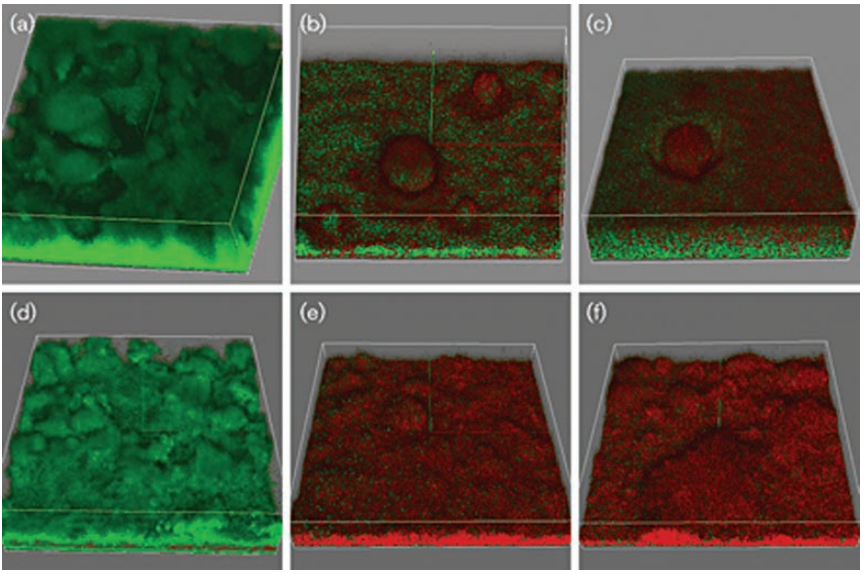



FIGURE 10.5. Treatment of *P. aeruginosa* biofilm with tobramycin. Wild-type PAO1 and Δ*lasRrhlR* mutant, both expressing green fluorescent protein (gfp) as a tag, were grown as biofilms in flow chambers for 3 days. On day 3 tobramycin 10 μg/ml and 20 μg/ml were added. Propidium iodide was added after day 3 to continuously monitor the killing of the biofilm by tobramycin. The figures show the biofilm after 48 hours of treatment. (a) Untreated wild-type; (b) 10 μg/ml wild-type; (c) 20 μg/ml wild-type; (d) untreated Δ*lasRrhlR* mutant; (e) 10 μg/ml Δ*lasRrhlR* mutant; (f) 20 μg/ml Δ*lasRrhlR* mutant (Bjarnsholt et al. 2005). Copyright Society for General Microbiology.

suggesting that oxygen limitation and low metabolic activity are more relevant to biofilm tolerance. However, in zones of the CF lung with poor access to aminoglycoside aerosols, where the antibiotic concentration is too low to saturate the exopolysaccharide matrix, delayed penetration of the aminoglycosides through thick biofilms might play a role in the tolerance of biofilms to aminoglycosides.

(2) As previously shown, tolerance of biofilms to tobramycin is mediated by starvation but the high cell density that results in accumulation of extracellular signalling molecules is also important. It has been shown that tolerance to tobramycin of PAO1 biofilm is quorum sensing mediated (Bjarnsholt et al. 2005) Figure 10.5

(3) A gene differently expressed in biofilms, *ndvB*, required for the synthesis of periplasmic glucans was shown to confer higher tolerance to tobramycin at least in one *P. aeruginosa* isolate, PA14 (Mah et al. 2003). However, this gene was not differently expressed in biofilm cells of *P. aeruginosa* PAO1 (Hentzer et al. 2005) and therefore it cannot be a general mechanism for tobramycin tolerance.

It has also been shown that subinhibitory concentrations of aminoglycosides induce biofilm formation in *P. aeruginosa* through a pathway involving cyclic diguanosine monophosphate (c-diGMP)—a bacterial second messenger that regulates cell-surface adhesiveness (Hoffman et al. 2005).

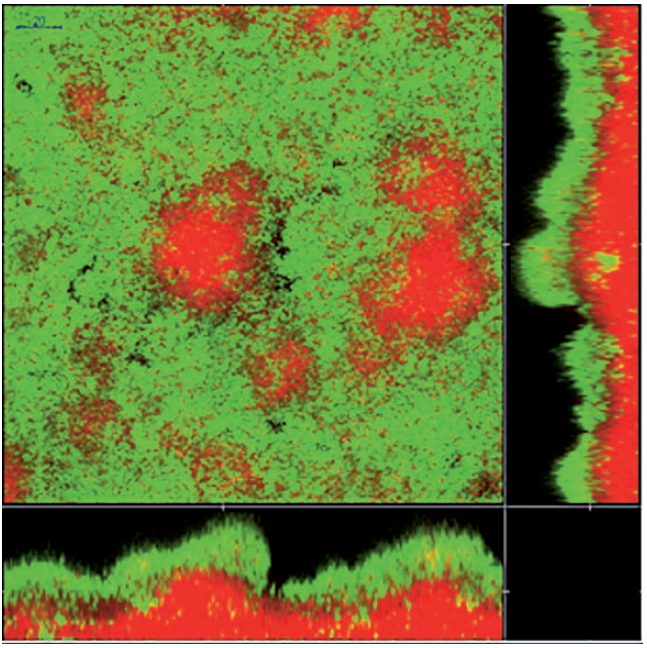


FIGURE 10.6. Treatment of *P. aeruginosa* biofilms with colistin. *P. aeruginosa* PAO1 expressing green fluorescent protein (gfp) as a tag were grown as biofilms in flow chambers for 4 days. Propidium iodide was added after day 4 to continuously monitor the killing of the biofilm by colistin. The figure shows the biofilm after 2 days of treatment with colistin 25 μg/ml. Images are courtesy of Janus Haagensen and Professor Søren Molin, Biocentrum, DTU, Lyngby, Denmark.

## *The Response of P. aeruginosa Biofilms to Polymyxins*

In contrast to the killing of biofilm cells by other antipseudomonal drugs, colistin killed the cells in the deeper layer of the biofilm while the superficial layers survived (Figure 10.6). This might be due to the potential of the metabolically active cells to upregulate the PhoP-PhoQ and PmrA-PmrB two-component regulatory systems involved in the adaptive resistance to cationic peptides.

This hypothesis is supported by the observation that the *pmr* mutation eliminates the tolerance of *P. aeruginosa* PAO1 biofilm to colistin (Haagensen et al, 2007). Quorum sensing does not seem to be involved in the tolerance of biofilm to colistin, as a similar pattern was observed when quorum sensing mutants *lasIrhlI* and *lasR-rhlR* were treated with colistin.

Combination therapy with ciprofloxacin that killed the superficial layers of the biofilm and colistin that killed the deeper layers of the biofilm showed good efficacy against *P. aeruginosa* PAO1 flow-cell biofilm (Figure 10.7).

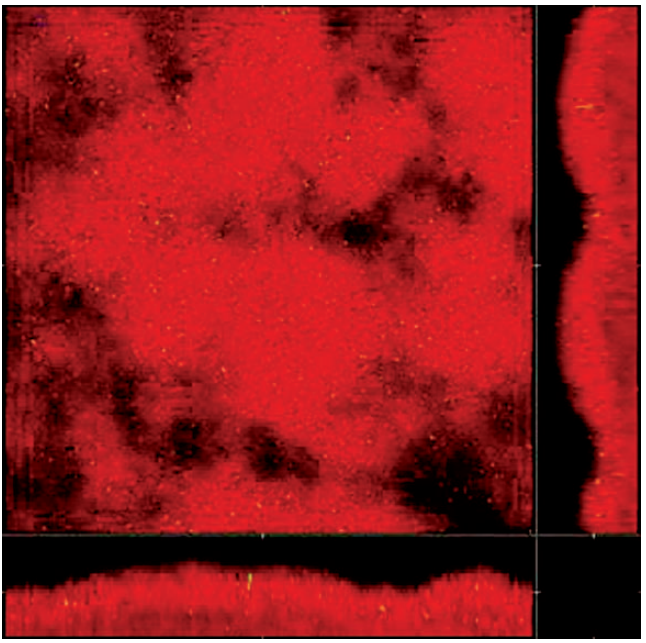


FIGURE 10.7. Treatment of *P. aeruginosa* biofilm with a combination of ciprofloxacin and colistin. *P. aeruginosa* PAO1 expressing green fluorescent protein (gfp) as a tag were grown as biofilms in flow chambers for 4 days. Propidium iodide was added after day 4 to continuously monitor the killing of the biofilm by ciprofloxacin and colistin. The figure shows the biofilm after 2 days of treatment with 10 μg/ml ciprofloxacin and 25 μg/ml colistin. Images are courtesy of Janus Haagensen and Professor Søren Molin, Biocentrum, DTU, Lyngby, Denmark.

This result supports the data showing the clinical efficacy of this combination therapy for the early eradication treatment of *P. aeruginosa* in CF patients in the Copenhagen CF Center (Høiby et al. 2005).

## Oxidative Stress in the CF Lung and Hypermutability

Chronic lung infection in CF patients is a state of chronic oxidative stress (Wood et al. 2001, Lagrange-Puget et al. 2004).

PMNs release leukocyte proteases, myeloperoxidase, and reactive oxygen species (ROS) that are the main mechanisms of lung tissue damage in CF (Doring et al. 1986, Hull et al. 1997). The ROS liberated by leukocytes together with the endogenous oxygen species that occur during replication may increase the oxidative stress of the bacterial DNA. Oxidation of guanine, 8-oxo-2′-deoxyguanosine (8-oxodG) is a frequently encountered lesion. 8-oxodG promotes the misincorporation of adenine in the replication round, producing G:C to T:A mutations, thus making unrepaired 8-oxodG a highly mutagenic lesion.

Several mechanisms are involved in the repair of this mutagenic lesion represented by the GO system. Mutations in the GO system genes increase the number of 8-oxodG molecules and the mutation frequency of the isolates. We showed that the oxidative damage of the bacterial DNA is increased in hypermutable compared to nonhypermutable *P. aeruginosa*. In addition, increased levels of DNA oxidation were found after exposure of the reference strain PAO1 to activated PMNs compared to controls (Ciofu et al. 2005).

It is, therefore, likely that oxidation of DNA by activated PMN during chronic inflammation in the CF lung is an initial event in the development of hypermutable strains.

Strains with high levels of 8-oxodG will have an increased risk of occurrence of mutations in genes involved in DNA repair, and subsequently emergence of hypermutable isolates.

## How to Cope with Resistant *P. aeruginosa* in the CF Lung

### *Preventing Biofilm Formation and Suppressing Biofilm Infection*

The primary treatment aim is to prevent chronic mucoid *P. aeruginosa* infection in the lungs by early aggressive therapy of intermittent colonization with nonmucoid phenotypes and to direct the therapy in chronically infected patients against the mucoid phenotype and not pay too much attention to the presence of multiply resistant nonmucoid phenotypes of *P. aeruginosa*. Such a strategy has been used successfully in the Danish CF Center since 1989 (Høiby et al. 2005).

## *Preventing Infection with P. aeruginosa by Cohorting Infected and Noninfected CF Patients*

Chronically infected patients constitute a major microbial reservoir from which noninfected patients can be infected with both *P. aeruginosa* and *B. cepacia* complex by direct patient-to-patient transmission, and possibly also by exposure to contaminated environments. Other more rare pathogens such as *Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, and nontuberculous mycobacteria (NTM) appear less capable of causing patient-to-patient transmission. Both the physical proximity and the duration of exposure of noninfected patients to patients chronically infected with *P. aeruginosa* and *B. cepacia* complex are important determinants of the risk of cross-infection. Cohorting of patients according to presence or absence of specific pathogens coupled with conventional hygienic precautions can, however, lead to a decrease in incidence and prevalence of chronic infections with these two species, and patient cohorting thus has become an integral component of infection control in patients with CF (Høiby et al. 2005).

## *Coping with Biofilm Related Resistance Mechanisms*

Biofilm susceptibility testing of 100 CF isolates demonstrated diminished activity of several antipseudomonal antibiotics compared to standard *in vitro* susceptibility testing and suggests that the use of standard drug dosages results in suboptimal drug concentrations at the site of infection (Moskowitz et al. 2004).

The negative effects of sub-MIC concentrations are multiple: lack of bacterial killing, development of antibiotic resistance due to exposure of bacterial cells at concentrations lower than the mutant preventing concentration, and enhancement of biofilm formation. It has been shown that sub-MIC concentrations of aminoglycosides (Hoffman et al. 2005), β-lactam antibiotics (Bagge et al. 2004b) and quinolones (Takahashi et al. 1995) upregulate genes involved in biofilm formation. Taking into account the enhanced potential of biofilm bacteria to mutate due to transient hypermutability, the window of occurrence of mutations in biofilm might be very broad. To circumvent occurrence of mutations causing antibiotic resistance in biofilm bacteria, high dosages of antibiotics and combination therapy should be used. For the biofilm in conductive zones of the airways, high antibiotic concentrations can be achieved by inhalations whereas intravenous treatment is employed for the biofilm in respiratory zones of the airways.

Due to the hypermutable subpopulations in a bacterial population of $10^7$ CFU/g sputum (Wong et al. 1984) growing in biofilm, it should be anticipated that mutants resistant to virtually all single antipseudomonal agents are already present in a high proportion of CF patients with chronic *P. aeruginosa* lung infection prior to treatment (Oliver et al. 2004). The direct consequence is that the use of combination therapy with pairs of antibiotics of different classes with synergistic activities should be applied at all stages of the infection, starting with early aggressive treatment as recommended in the European Consensus Document on Early Intervention and Prevention of Lung Disease in Cystic Fibrosis (Döring and Høiby 2004).

The role of quorum sensing system in biofilm formation has been established (Costerton et al. 1999) and its role in regulation of several virulence factors of *P. aeruginosa* (Passador et al. 1993) and its importance in the pathogenesis of *P. aeruginosa* infection have been demonstrated (Geisenberger et al. 2000, Singh et al. 2000). As previously mentioned, the tolerance of biofilms to several groups of antibiotics, such as β-lactams, aminoglycosides, and quinolones, was shown to be dependent on quorum sensing. Davies et al. (1998) demonstrated that a QS-deficient in *las I* mutant of *P. aeruginosa* formed biofilms that were more susceptible to biocides. Treatment of biofilms with quorum-sensing inhibitors, like furanones or garlic compounds, facilitated the eradication of *P. aeruginosa* biofilms by tobramycin and detergents (Rasmussen and Givskov 2006). Treatment of biofilms with combination of antibiotics and QS inhibitors will improve the eradication potential of antimicrobial agents.

Macrolides, which have no bacteriostatic effect on *P. aeruginosa in vitro* or *in vivo* when clinically attainable concentrations are used, have been proven to have a beneficial effect on lung function of CF patients with chronic *P. aeruginosa* infection (Equi et al. 2002, Wolter et al. 2002, Saiman et al. 2003). This can be explained by their multiple ways of action: destruction of the biofilm structure by decreasing the alginate production (Nagino and Kobayashi 1997), inhibition of the quorum sensing system (Tateda et al. 2001) that plays an important role in the biofilm formation and anti-inflammatory properties (Jaffe and Bush 2001).

## *Coping with Conventional Resistance Mechanisms*

To overcome the problem of overproduction of chromosomally encoded β-lactamases, an obvious therapeutic choice is the use of β-lactamase inhibitors. β-Lactamase inhibitors such as tazobactam in combination with piperacillin (Tazocin) are therapeutic alternatives for CF patients infected with resistant strains but their use is limited by the high percentage of CF patients with hypersensitivity to penicillins (Koch et al. 1991). Aztreonam has also been shown to inhibit chromosomal β-lactamase of *P. aeruginosa in vivo* in CF patients (Giwercman et al. 1992) and double β-lactam therapy with e.g. ceftazidime and aztreonam is sometimes used in the Danish CF Center. Other inhibitors such as BRL42715 and Syn2190 have shown promising results *in vitro* (Babini and Livermore 2000). These inhibitors, however, have a β-lactam ring in their structure and might easily be inactivated by the same resistance mechanisms that cause resistance to β-lactams. β-Lactamases that are inhibitor-resistant and efflux pumps able to eliminate β-lactamase inhibitors, like clavulanate, cloxacillin, and BRL42715, have already been described (Li et al. 1998, Bradford 2001). Non-β-lactam compound inhibitors that specifically and potently inhibit AmpC β-lactamases without induction of the enzyme have been developed (Powers et al. 2002, Tondi et al. 2005) and will be useful compounds when available on the market. Inhibition of

resistance gene expression by antisense molecules such as PNA (Good and Nielsen 1998) are promising alternative strategies in the future.

A novel therapeutic strategy would be the inhibition of β-lactamase by induction of neutralizing antibodies against β-lactamase (Ciofu et al. 2002) or by passive immunization of humanized monoclonal antibodies with β-lactamase neutralizing capacity that might be administered simultaneously with the β-lactam antibiotic and act as β-lactamase inhibitor. Other potential β-lactamase inhibitors are single-domain antibody fragments elicited in the Camelidae as published by Conrath et al. (2001).

The use of efflux pump inhibitors (EPI) like MC-04, 124 (Kriengkauykiat et al. 2005) might be useful in combination therapy especially with quinolones, as overexpression of efflux pump was often found in quinolone resistant *P. aeruginosa* from CF patients (Jalal et al. 2000) and was rapidly selected in animal models of hypermutable *P. aeruginosa* infection under treatment with ciprofloxacin (Macia et al. 2006).

## *Coping with Oxidative Stress*

An obvious strategy to prevent the occurrence of hypermutable isolates due to the oxidative damage of the DNA is the use of antioxidants. Chopra et al. (2003) showed that addition of antioxidants to cultures of hypermutable *E. coli* reduced the mutation frequency. The oxidative stress in the CF lung is determined by the large number of activated PMNs in the respiratory airways but also by the deficiency in the anti-oxidant systems, like reduced glutathione. It has been shown that glutathione aerosols delivered to patients with CF suppress the oxidative burden on the surface of lung epithelial cells (Roum et al. 1999). We have previously shown that *N*-acetylcysteine can decrease the oxidative burst of PMNs and monocytes and that this drug has a positive influence on the clinical condition of CF patients with chronic *P. aeruginosa* infection (Jensen et al. 1988, Stafanger and Koch 1989).

Experiments are in progress to investigate the use of *N*-acetylcysteine for prevention of hypermutability and of antibiotic resistance development in *P. aeruginosa*.

## *References*

Alonso A, Campanario E, Martinez JL. 1999. Emergence of multidrug-resistant mutants is increased under antibiotic selective pressure in *Pseudomonas aeruginosa*. Microbiology 145:2857–2862.

Anwar H, Costerton JW. 1990. Enhanced activity of combination of tobramycin and piperacillin for eradication of sessile biofilm cells of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 34:1666–1671.

Anwar H, Strap JL, Costerton JW. 1992. Establishment of aging biofilms: Possible mechanism of bacterial resistance to antimicrobial therapy. Antimicrob Agents Chemother 36:1347–1351.

Babini GS, Livermore DM. 2000. Effect of conalbumin on the activity of Syn 2190, a 1,5 dihydroxy-4-pyridon monobactam inhibitor of AmpC beta-lactamases. J Antimicrob Chemother 45:105–109.

Bagge N, Ciofu O, Hentzer M, Campbell JI, Givskov M, Høiby N. 2002. Constitutive high expression of chromosomal beta-lactamase in *Pseudomonas aeruginosa* caused by a new insertion sequence (IS1669) located in ampD. Antimicrob Agents Chemother 46:3406–3411.

Bagge N, Hentzer M, Andersen JB, Ciofu O, Givskov M, Høiby N. 2004a. Dynamics and spatial distribution of beta-lactamase expression in *Pseudomonas aeruginosa* biofilms. Antimicrob Agents Chemother 48:1168–1174.

Bagge N, Schuster M, Hentzer M, Ciofu O, Givskov M, Greenberg EP, Høiby N. 2004b. *Pseudomonas aeruginosa* biofilms exposed to imipenem exhibit changes in global gene expression and beta-lactamase and alginate production. Antimicrob Agents Chemother 48:1175–1187.

Ballestero S, Escobar H, Villaverde R, Elia M, Ojeda-Vargas M, Baquero F. 1993. Continuous monitoring of antimicrobial resistance in cystic fibrosis patients, in Escobar H, Baquero F, Suarez L (eds). Clinical Ecology of Cystic Fibrosis. Madrid, Elsevier Science Publishers, pp 63–72.

Barclay ML, Begg EJ, Chambers ST, Thornley PE, Pattemore PK, Grimwood K. 1996. Adaptive resistance to tobramycin in *Pseudomonas aeruginosa* lung infection in cystic fibrosis. J Antimicrob Chemother 37:1155–1164.

Bjarnsholt T, Jensen PO, Burmolle M, Hentzer M, Haagensen JA, Hougen HP, Calum H, Madsen KG, Moser C, Molin S, Høiby N, Givskov M. 2005. *Pseudomonas aeruginosa* tolerance to tobramycin, hydrogen peroxide and polymorphonuclear leukocytes is quorum-sensing dependent. Microbiology 151:373–383.

Blázquez J, Gómez-Gómez J M, Oliver A, Juaz C, kapur V, Martins. 2006. $PBP_3$ inhibition elicits adapture responses in *Pseudomomas arruginosa* Mol. Microbiol 62:84–99.

Borriello G, Werner E, Roe F, Kim AM, Ehrlich GD, Stewart PS. 2004. Oxygen limitation contributes to antibiotic tolerance of *Pseudomonas aeruginosa* in biofilms. Antimicrob Agents Chemother 48:2659–2664.

Bradford PA. 2001. Extended-spectrum beta-lactamases in the 21st century: Characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 14:933–951, table of contents.

Chopra I, O'Neill AJ, Miller K. 2003. The role of mutators in the emergence of antibiotic-resistant bacteria. Drug Resist Updat 6:137–145.

Ciofu O. 2003. *Pseudomonas aeruginosa* chromosomal beta-lactamase in patients with cystic fibrosis and chronic lung infection. Mechanism of antibiotic resistance and target of the humoral immune response. APMIS Suppl:1–47.

Ciofu O, Beveridge TJ, Kadurugamuwa J, Walther-Rasmussen J, Høiby N. 2000. Chromosomal beta-lactamase is packaged into membrane vesicles and secreted from *Pseudomonas aeruginosa*. J Antimicrob Chemother 45:9–13.

Ciofu O, Fussing V, Bagge N, Koch C, Høiby N. 2001. Characterization of paired mucoid/non-mucoid *Pseudomonas aeruginosa* isolates from Danish cystic fibrosis patients: Antibiotic resistance, beta-lactamase activity and RiboPrinting. J Antimicrob Chemother 48:391–396.

Ciofu O, Bagge N, Høiby N. 2002. Antibodies against beta-lactamase can improve ceftazidime treatment of lung infection with beta-lactam-resistant *Pseudomonas aeruginosa* in a rat model of chronic lung infection. APMIS 110:881–891.

Ciofu O, Riis B, Pressler T, Poulsen HE, Høiby N. 2005. Occurrence of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis patients is associated with the oxidative stress caused by chronic lung inflammation. Antimicrob Agents Chemother 49:2276–2282.

Conrath KE, Lauwereys M, Galleni M, Matagne A, Frere JM, Kinne J, Wyns L, Muyldermans S. 2001. Beta-lactamase inhibitors derived from single-domain antibody fragments elicited in the Camelidae. Antimicrob Agents Chemother 45:2807–2812.

Costerton JW, Stewart PS, Greenberg EP. 1999. Bacterial biofilms: A common cause of persistent infections. Science 284:1318–1322.

Davies D, Parsek M, Pearson J, Iglewski B, Costerton JW, Greenberg EP. 1998. The involvement of cell-to-cell signals in the development of bacterial biofilms. Science 280:295–298.

De Kievit TR, Parkins MD, Gillis RJ, Srikumar R, Ceri H, Poole K, Iglewski BH, Storey DG. 2001. Multidrug efflux pumps: Expression patterns and contribution to antibiotic resistance in *Pseudomonas aeruginosa* biofilms. Antimicrob Agents Chemother 45:1761–1770.

Döring G, Høiby N. 2004. Early intervention and prevention of lung disease in cystic fibrosis: A European consensus. J Cyst Fibros 3:67–91.

Döring G, Goldstein W, Botzenhart K, Kharazmi A, Schiøtz PO, Høiby N, Dasgupta M. 1986. Elastase from polymorphonuclear leucocytes: A regulatory enzyme in immune complex disease. Clin Exp Immunol 64:597–605.

Drenkard E, Ausubel FM. 2002. Pseudomonas biofilm formation and antibiotic resistance are linked to phenotypic variation. Nature 416:740–743.

Drlica K, Zhao X. 1997. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev 61:377–392.

Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. 2002. Long term azithromycin in children with cystic fibrosis: A randomised, placebo-controlled crossover trial. Lancet 360:978–984.

Frederiksen B, Koch C, Høiby N. 1999. Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974–1995). Pediatr Pulmonol 28:159–166.

Friedberg EC, Walker GC, Siede W. 1995. DNA Repair and Mutagenesis. Washington, DC, ASM Press.

Fux CA, Costerton JW, Stewart PS, Stoodley P. 2005. Survival strategies of infectious biofilms. Trends Microbiol 13:34–40.

Geisenberger O, Givskov M, Riedel K, Høiby N, Tummler B, Eberl L. 2000. Production of N-acyl-L-homoserine lactones by *P. aeruginosa* isolates from chronic lung infections associated with cystic fibrosis. FEMS Microbiol Lett 184:273–278.

Giwercman B, Lambert PA, Rosdahl VT, Shand GH, Høiby N. 1990. Rapid emergence of resistance in *Pseudomonas aeruginosa* in cystic fibrosis patients due to in-vivo selection of stable partially derepressed beta-lactamase producing strains. J Antimicrob Chemother 26:247–259.

Giwercman B, Jensen ET, Høiby N, Kharazmi A, Costerton JW. 1991. Induction of beta-lactamase production in *Pseudomonas aeruginosa* biofilm. Antimicrob Agents Chemother 35:1008–1010.

Giwercman B, Meyer C, Lambert PA, Reinert C, Høiby N. 1992. High-level beta-lactamase activity in sputum samples from cystic fibrosis patients during antipseudomonal treatment. Antimicrob Agents Chemother 36:71–76.

Good L, Nielsen PE. 1998. Antisense inhibition of gene expression in bacteria by PNA targeted to mRNA. Nat Biotechnol 16:355–358.

Haagensen J.A, Klausen M, Ernst R, Miller S.I, Folkesson A, Tolker Nielsen T, Malin S. 2007. Differentiation and distribution of Colistin and Sodium Dodecyl Sulfate Tolerant cells in *Pseudomonas aeruginosa* biofilms. J. Bacterial 189:28–37.

Hancock RE, Raffle VJ, Nicas TI. 1981. Involvement of the outer membrane in gentamicin and streptomycin uptake and killing in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 19:777–785.

Hentzer M, Eberl L, Givskov M. 2005. Transcriptome analysis of *Pseudomonas aeruginosa* biofilm development: Anaerobic respiration and iron limitation. Biofilms 2:37–61.

Hill D, Rose B, Pajkos A, Robinson M, Bye P, Bell S, Elkins M, Thompson B, Macleod C, Aaron SD, Harbour C. 2005. Antibiotic susceptibilities of *Pseudomonas aeruginosa* isolates derived from patients with cystic fibrosis under aerobic, anaerobic, and biofilm conditions. J Clin Microbiol 43:5085–5090.

Hoffman LR, D'Argenio DA, MacCoss MJ, Zhang Z, Jones RA, Miller SI. 2005. Aminoglycoside antibiotics induce bacterial biofilm formation. Nature 436:1171–1175.

Høiby N, Krogh Johansen H, Moser C, Song Z, Ciofu O, Kharazmi A. 2001. *Pseudomonas aeruginosa* and the in vitro and in vivo biofilm mode of growth. Microbes Infect 3:23–35.

Høiby N, Frederiksen B, Pressler T. 2005. Eradication of early *Pseudomonas aeruginosa* infection. J Cyst Fibros 4 Suppl 2:49–54.

Hull J, Vervaart P, Grimwood K, Phelan P. 1997. Pulmonary oxidative stress response in young children with cystic fibrosis. Thorax 52:557–560.

Jaffe A, Bush A. 2001. Anti-inflammatory effects of macrolides in lung disease. Pediatr Pulmonol 31:464–473.

Jalal S, Ciofu O, Høiby N, Gotoh N, Wretlind B. 2000. Molecular mechanisms of fluoroquinolone resistance in *Pseudomonas aeruginosa* isolates from cystic fibrosis patients. Antimicrob Agents Chemother 44:710–712.

Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. 1987. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. J Antimicrob Chemother 19:831–838.

Jensen T, Kharazmi A, Schiøtz PO, Nielsen H, Stenvang Pedersen S, Stafanger G, Koch C, Høiby N. 1988. Effect of oral N-acetylcysteine administration on human blood neutrophil and monocyte function. APMIS 96:62–67.

Johansen HK, Ciofu O, Koch C, Høiby N. 2003. Emergence and elimination of colistin resistant *Pseudomonas aeruginosa* in chronically infected Danish cystic fibrosis patients. In: 26th European Cystic Fibrosis Conference, Belfast, Northen Ireland.

Karlowsky JA, Saunders MH, Harding GA, Hoban DJ, Zhanel GG. 1996. In vitro characterization of aminoglycoside adaptive resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 40:1387–1393.

Katsorchis T, Legakis NJ, Shearer B, Genmmata V, Pataryas H. 1985. Outer surface changes of *Pseudomonas aeruginosa* in relation to resistance to gentamicin and carbenicillin. J Med Microbiol 19:375–381.

Koch C, Hjelt K, Pedersen SS, Jensen ET, Jensen T, Lanng S, Valerius NH, Pedersen M, Høiby N. 1991. Retrospective clinical study of hypersensitivity reactions to aztreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple treatment courses. Rev Infect Dis 13 Suppl 7:S608–611.

Kriengkauykiat J, Porter E, Lomovskaya O, Wong-Beringer A. 2005. Use of an efflux pump inhibitor to determine the prevalence of efflux pump-mediated fluoroquinolone resistance and multidrug resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 49:565–570.

Lagrange-Puget M, Durieu I, Ecochard R, Abbas-Chorfa F, Drai J, Steghens JP, Pacheco Y, Vital-Durand D, Bellon G. 2004. Longitudinal study of oxidative status in 312 cystic

fibrosis patients in stable state and during bronchial exacerbation. Pediatr Pulmonol 38:43–49.

LeClerc JE, Li B, Payne WL, Cebula TA. 1996. High mutation frequencies among *Escherichia coli* and Salmonella pathogens. Science 274:1208–1211.

Li XZ, Zhang L, Srikumar R, Poole K. 1998. Beta-lactamase inhibitors are substrates for the multidrug efflux pumps of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 42:399–403.

Macfarlane EL, Kwasnicka A, Hancock RE. 2000. Role of *Pseudomonas aeruginosa* PhoP-phoQ in resistance to antimicrobial cationic peptides and aminoglycosides. Microbiology 146 (Pt 10):2543–2554.

Macia MD, Borrell N, Segura M, Gomez C, Perez JL, Oliver A. 2006. Efficacy and potential for resistance selection of antipseudomonal treatments in a mouse model of lung infection by hypermutable *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 50:975–983.

MacLeod DL, Nelson LE, Shawar RM, Lin BB, Lockwood LG, Dirk JE, Miller GH, Burns JL, Garber RL. 2000. Aminoglycoside-resistance mechanisms for cystic fibrosis *Pseudomonas aeruginosa* isolates are unchanged by long-term, intermittent, inhaled tobramycin treatment. J Infect Dis 181:1180–1184.

Mah TF, Pitts B, Pellock B, Walker GC, Stewart PS, O'Toole GA. 2003. A genetic basis for *Pseudomonas aeruginosa* biofilm antibiotic resistance. Nature 426:306–310.

McPhee JB, Lewenza S, Hancock RE. 2003. Cationic antimicrobial peptides activate a two-component regulatory system, PmrA-PmrB, that regulates resistance to polymyxin B and cationic antimicrobial peptides in *Pseudomonas aeruginosa*. Mol Microbiol 50:205–217.

Miller C, Thomsen LE, Gaggero C, Mosseri R, Ingmer H, Cohen SN. 2004. SOS response induction by beta-lactams and bacterial defense against antibiotic lethality. Science 305:1629–1631.

Moskowitz SM, Burns JL, Nguyen CD, Høiby N, Ernst RK, Miller SI. 2000. Polymyxin resistance and lipid A structure of *Pseudomonas aeruginosa* isolated from colistin-treated and colistin-naive cystic fibrosis patients. Pediatr Pulmonol Suppl 20:272.

Moskowitz SM, Foster JM, Emerson J, Burns JL. 2004. Clinically feasible biofilm susceptibility assay for isolates of *Pseudomonas aeruginosa* from patients with cystic fibrosis. J Clin Microbiol 42:1915–1922.

Murakami K, Ono T, Viducic D, Kayama S, Mori M, Hirota K, Nemoto K, Miyake Y. 2005. Role for rpoS gene of *Pseudomonas aeruginosa* in antibiotic tolerance. FEMS Microbiol Lett 242:161–167.

Nagino K, Kobayashi H. 1997. Influence of macrolides on mucoid alginate biosynthetic enzyme from *Pseudomonas aeruginosa*. Clin Microbiol Infect 3:432–439.

Nakae T, Nakajima A, Ono T, Saito K, Yoneyama H. 1999. Resistance to beta-lactam antibiotics in *Pseudomonas aeruginosa* due to interplay between the MexAB-OprM efflux pump and beta-lactamase. Antimicrob Agents Chemother 43:1301–1303.

Nichols WW, Evans MJ, Slack MP, Walmsley HL. 1989. The penetration of antibiotics into aggregates of mucoid and non-mucoid *Pseudomonas aeruginosa*. J Gen Microbiol 135:1291–1303.

Nickel JC, Ruseska I, Wright JB, Costerton JW. 1985. Tobramycin resistance of *Pseudomonas aeruginosa* cells growing as a biofilm on urinary catheter material. Antimicrob Agents Chemother 27:619–624.

Oliver A, Canton R, Campo P, Baquero F, Blazquez J. 2000. High frequency of hypermutable *Pseudomonas aeruginosa* in cystic fibrosis lung infection. Science 288:1251–1254.

Oliver A, Levin BR, Juan C, Baquero F, Blazquez J. 2004. Hypermutation and the preexistence of antibiotic-resistant *Pseudomonas aeruginosa* mutants: Implications for susceptibility testing and treatment of chronic infections. Antimicrob Agents Chemother 48:4226–4233.

Passador L, Cook JM, Gambello MJ, Rust L, Iglewski BH. 1993. Expression of *Pseudomonas aeruginosa* virulence genes requires cell-to-cell communication. Science 260:1127–1130.

Pedersen SS, Høiby N, Espersen F, Koch C. 1992. Role of alginate in infection with mucoid *Pseudomonas aeruginosa* in cystic fibrosis. Thorax 47:6–13.

Powers RA, Morandi F, Shoichet BK. 2002. Structure-based discovery of a novel, noncovalent inhibitor of AmpC beta-lactamase. Structure 10:1013–1023.

Radman M, Taddei F, Matic I. 2000. Evolution-driving genes. Res Microbiol 151:91–95.

Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev KM, Borowitz D, Bowman CM, Marshall BC, Marshall S, Smith AL. 1999. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 340:23–30.

Rasmussen TB, Givskov M. 2006. Quorum sensing inhibitors: A bargain of effects. Microbiology 152:895–904.

Roum JH, Borok Z, McElvaney NG, Grimes GJ, Bokser AD, Buhl R, Crystal RG. 1999. Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. J Appl Physiol 87:438–443.

Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd. 2003. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa:* A randomized controlled trial. JAMA 290:1749–1756.

Sanders CC, Gates ML, Sanders WE Jr. 1988. Heterogeneity of class I beta-lactamase expression in clinical isolates of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 32:1893–1895.

Shawar RM, MacLeod DL, Garber RL, Burns JL, Stapp JR, Clausen CR, Tanaka SK. 1999. Activities of tobramycin and six other antibiotics against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 43:2877–2880.

Shearer BG, Legakis NJ. 1985. *Pseudomonas aeruginosa*: Evidence for the involvement of lipopolysaccharide in determining outer membrane permeability to carbenicillin and gentamicin. J Infect Dis 152:351–355.

Singh PK, Schaefer AL, Parsek MR, Moninger TO, Welsh MJ, Greenberg EP. 2000. Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature 407:762–764.

Stafanger G, Koch C. 1989. N-acetylcysteine in cystic fibrosis and *Pseudomonas aeruginosa* infection: Clinical score, spirometry and ciliary motility. Eur Respir J 2:234–237.

Taddei F, Radman M, Maynard-Smith J, Toupance B, Gouyon PH, Godelle B. 1997. Role of mutator alleles in adaptive evolution. Nature 387:700–702.

Takahashi A, Yomoda S, Ushijima Y, Kobayashi I, Inoue M. 1995. Ofloxacin, norfloxacin and ceftazidime increase the production of alginate and promote the formation of biofilm of *Pseudomonas aeruginosa* in vitro. J Antimicrob Chemother 36:743–745.

Tanaka G, Shigeta M, Komatsuzawa H, Sugai M, Suginaka H, Usui T. 1999. Effect of the growth rate of *Pseudomonas aeruginosa* biofilms on the susceptibility to antimicrobial agents: Beta-lactams and fluoroquinolones. Chemotherapy 45:28–36.

Tateda K, Comte R, Pechere JC, Kohler T, Yamaguchi K, Van Delden C. 2001. Azithromycin inhibits quorum sensing in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 45:1930–1933.

Thomassen MJ, Demko CA, Boxerbaum B, Stern RC, Kuchenbrod PJ. 1979. Multiple of isolates of *Pseudomonas aeruginosa* with differing antimicrobial susceptibility patterns from patients with cystic fibrosis. J Infect Dis 140:873–880.

Tondi D, Morandi F, Bonnet R, Costi MP, Shoichet BK. 2005. Structure-based optimization of a non-beta-lactam lead results in inhibitors that do not up-regulate beta-lactamase expression in cell culture. J Am Chem Soc 127:4632–4639.

Valerius NH, Koch C, Høiby N. 1991. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. Lancet 338:725–726.

Vogne C, Aires JR, Bailly C, Hocquet D, Plesiat P. 2004. Role of the multidrug efflux system MexXY in the emergence of moderate resistance to aminoglycosides among *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 48:1676–1680.

Walsh TR, Toleman MA, Poirel L, Nordmann P. 2005. Metallo-beta-lactamases: The quiet before the storm? Clin Microbiol Rev 18:306–325.

Walters MC 3rd, Roe F, Bugnicourt A, Franklin MJ, Stewart PS. 2003. Contributions of antibiotic penetration, oxygen limitation, and low metabolic activity to tolerance of *Pseudomonas aeruginosa* biofilms to ciprofloxacin and tobramycin. Antimicrob Agents Chemother 47:317–323.

Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. 2002. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: A randomised trial. Thorax 57:212–216.

Wong K, Roberts MC, Owens L, Fife M, Smith AL. 1984. Selective media for the quantitation of bacteria in cystic fibrosis sputum. J Med Microbiol 17:113–119.

Wood LG, Fitzgerald DA, Gibson PG, Cooper DM, Collins CE, Garg ML. 2001. Oxidative stress in cystic fibrosis: Dietary and metabolic factors. J Am Coll Nutr 20:157–165.

Wood LF, Leech AJ, Ohman DE. 2006. Cell wall-inhibitory antibiotics activate the alginate biosynthesis operon in *Pseudomonas aeruginosa*: Roles of sigma (AlgT) and the AlgW and Prc proteases. Mol Microbiol 62:412–426.

Yamane K, Doi Y, Yokoyama K, Yagi T, Kurokawa H, Shibata N, Shibayama K, Kato H, Arakawa Y. 2004. Genetic environments of the rmtA gene in *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 48:2069–2074.

# Chapter 11
# Community-Acquired Pneumonia—Back to Basics

Marc J. M. Bonten and Jan Jelrik Oosterheert

## Background

Lower respiratory tract infections are among the most common infectious diseases worldwide and are caused by the inflammation and consolidation of lung tissue due to an infectious agent.[1] The clinical criteria for the diagnosis include chest pain, cough, auscultatory findings such as rales or evidence of pulmonary consolidation, fever, or leukocytosis. Radiographic evidence, such as the presence of new infiltrates on chest radiograph, and laboratory evidence can support the diagnosis.[2] Elderly and patients with underlying conditions, such as cerebro- and cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and alcoholism, are at increased risk for developing lower respiratory tract infections and complicated courses of infection.[3, 4] Complications include the development of progressive pneumonia, pleural empyema, uncontrolled sepsis, and death, sometimes even despite appropriate antimicrobial treatment.[5]

Because of differences in pathogenesis and causative microorganisms, healthcare-associated and community-acquired pneumonia (CAP) are usually distinguished. CAP represents a broad spectrum of disease severity, ranging from mild pneumonia that can be managed by general practitioners to severe pneumonia with septic shock needing treatment in the intensive care unit (ICU). Most cases of CAP are successfully managed in primary care and approximately 20 and 1% of patients need hospitalization or treatment in ICU, respectively.[6, 7]

Despite the widespread availability of antibiotics and reduced mortality since their introduction, lower respiratory tract infections remain the most important infectious cause of death in the developed world.[8] For instance, absolute mortality due to pneumonia has increased in the past 10 years in the Netherlands and the United States.[8–12]

Estimated annual costs for treating CAP were in excess of 1 billion US$ in the United Kingdom in 1997 and 9.7 billion US$ in the United States in 2001.[8, 13–15]

Lower respiratory tract infections are most frequently caused by bacteria or viruses. Treatment should be directed toward the causative organisms, with antibiotics prescribed only for bacterial infections and being withheld for

nonbacterial causes of inflammation. Yet, causative agents have usually not been identified at the time that treatment must be initiated and empirical therapy should, therefore, cover the most likely pathogens. This implies that it is unavoidable that empirical therapy frequently includes a wider range of pathogens and, thus, a broader antibiotic spectrum than a choice that exclusively covers the pathogen involved.

On a population level, the quantity of antibiotics prescribed is linearly related to antibiotic resistance and unnecessary antibiotic use should, therefore, be prevented. Despite this paradigm, overuse of antibiotics frequently occurs, especially in case of viral infections.[16] Yet, this goal to minimize unnecessary antibiotic use must be balanced constantly against the urge to cover all potential pathogens in order to prescribe optimal treatment for the individual patient. Therefore, optimizing therapeutic efficacy of empirical treatment, while preventing unnecessary antibiotic use have become important issues in the management of lower respiratory tract infections. In this chapter, etiologic, diagnostic, therapeutic, and preventive considerations are described to optimize antibiotic prescription for the individual patient with lower respiratory tract infections, while keeping antibiotic resistance development on a population level in mind.

## Etiology

Worldwide, *Streptococcus pneumoniae* is by far the most important pathogen for CAP. Other frequently isolated bacteria are *Haemophilus influenzae* and *Staphylococcus aureus*.[17–23] Incidences of atypical pathogens, such as *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila*, are generally lower than those of the afore-mentioned bacteria, although variations may be large.[17, 18, 20, 23] *Pseudomonas aeruginosa* can be relevant in patients with structural lung damage, such as those with bronchiectasis or COPD.[24] Most frequent viral causes of CAP include influenza virus and parainfluenza virus.[23, 25] Viral pneumonias due to infection with influenza, respiratory syncytial virus, coronaviruses, parainfluenza virus, and even rhinoviruses can be life threatening in elderly and immunocompromised patients. Influenza pneumonia may be complicated by secondary bacterial infections caused by *S. aureus, S. pneumoniae, H. influenzae*, or other Gram- negative pathogens.[21, 26]

Recently, coronaviruses have been recognized as causes of severe lower respiratory tract infections. The SARS coronavirus caused severe CAP associated with high mortality rates, even in previously healthy adults.[27, 28] Non-SARS coronaviruses such as the coronavirus OC43 have been associated with lower respiratory tract infections in children and adults.[25, 29–31] Human metapneumovirus is increasingly recognized as a cause of respiratory failure in children and of pneumonia in the elderly.[32, 33] Importantly, up to 60% of episodes of CAP remain of unknown etiology.[6]

## Identification of Causative Pathogens

Rapid and reliable diagnostic results are needed for a prudent and pathogen-tailored antibiotic strategy. Currently available methods for etiological diagnosis include clinical, radiological, and laboratory findings, Gram staining of sputum, urinary antigen tests, or specific DNA detection using real-time polymerase chain reactions (PCR).

### *Clinical, Radiological, and Laboratory Features*

Although some clinical features have been associated with specific causative microorganisms—such as high fever, acute onset of disease, chills, productive cough, and thoracic pain with *S. pneumoniae*, and preceding influenza with *S. aureus*—there is consensus that in most cases, the microbial cause of CAP cannot be predicted using clinical or radiographic features.[34–38] New opportunities include the use of systemic levels of C-reactive protein (CRP) and procalcitonin (PCT). Yet, although raised CRP and PCT levels have been claimed to be indicative for bacterial infections, CRP levels could not differentiate between bacterial and viral respiratory tract infections in adults,[39] nor could PCT in children admitted with CAP.[40, 41] From another perspective, though, PCT was used to reduce unnecessary antibiotic prescriptions in patients with clinical symptoms of LRTI, without subsequent adverse effect on patient outcomes. Of note, reduction of antibiotic use was primarily achieved through withholding of antimicrobial therapy for patients with acute bronchitis and only 36% of patients had CAP in this study.[42]

### *Microbiology and Serology*

Routine diagnostic procedures to identify causative microorganisms include microbiological culturing of blood and sputum and serological testing of acute and reconvalescent blood samples. However, the clinical value of these conventional diagnostic methods in guiding treatment of CAP is limited because of low sensitivity and considerable delay.[43–47] Culturing other samples for which more invasive procedures are needed, such as pleural and bronchoalveolar fluids, might increase diagnostic yields, but inherently suffer from the same diagnostic delay. In one study, fiberoptic bronchoscopy provided an etiological diagnosis in 25% of patients in whom conventional diagnostic methods failed to identify a causative microorganism.[48] Yet, pathogen-directed empirical therapy in this study was not associated with better clinical outcome of patients.[49] Fiberoptic bronchoscopy should, therefore, be considered for cases of treatment failure without identified causative microorganism from conventional diagnostics. Importantly, even in study settings with extensive diagnostic testing, approximately 50% of episodes of CAP remain of unknown etiology[17–23, 34–37]

The use of sputum Gram staining in the diagnostic workup of CAP is controversial: its use is recommended by the Infectious Diseases Society of America

(IDSA), but not by the American Thoracic Society (ATS).[50, 51] Advantages of sputum Gram staining include its wide availability and low costs. However, adequate sputum samples cannot always be obtained, either because there is no sputum production or because samples are not adequate for evaluation. Furthermore, sensitivity and specificity are unknown, some bacteria cannot be identified, and a uniform definition of a positive stain does not exist.[45, 46]

### *Urinary Antigen Testing*

Two urinary antigen tests are available for diagnosing the microbial cause of CAP. The NOW *S. pneumoniae* urinary antigen test (Binax, Inc., Portland, Maine) detects, within 15 minutes, the C polysaccharide wall antigen common to all *S. pneumoniae* strains.[52] One study reported 90–100% specificity and 74% sensitivity.[53] Yet, specificity might be reduced due to nasopharyngeal carriage of pneumococci.[54]

The other urinary antigen test detects *L. pneumophila* type I and test accuracy increases with severity of disease, with sensitivities varying from approximately 40% in mild to 95% in severe CAP.[55] Immediate (within 24 hours after hospital admission) therapy for Legionnaires' disease, as detected by this test, increased ICU-free survival as compared to therapy initiated after $>$ 24 hours.[56]

### *DNA Detection*

Another approach is to identify viruses and "atypical" bacterial pathogens in respiratory samples through molecular techniques, such as polymerase chain reaction (PCR). Novel real-time Taq-Man PCR techniques are sensitive and specific and able to detect respiratory viruses in clinical specimens within hours.[25, 57] Yet, in a randomized trial, addition of real-time PCR analysis of respiratory viruses and atypical pathogens in nose and throat swabs to routine diagnostic workup, improved diagnostic yields but failed to reduce antibiotic use or healthcare-associated costs among patients admitted with lower respiratory tract infections (of whom 50% had CAP).[58]

## Therapy

### *Microorganisms and Antibiotic Resistance*

A detailed description of the underlying mechanisms of antibiotic resistance is beyond the scope of this chapter. In brief, alterations in the bacterial proteins that bind penicillin can decrease binding affinity and antimicrobial susceptibility to penicillins in *S. pneumoniae*. Such strains are also more likely to be resistant to other antibiotics, such as macrolides, tetracyclins, and fluoroquinolones. For the treatment of pneumococcal pneumonia, β-lactam antibiotic concentrations should exceed the MIC for at least 40% of the time.[59] When strains with reduced

susceptibility to penicillin are anticipated, this can be achieved with higher dosages of penicillin (e.g., 2 million units q 6 hours) or amoxicillin (e.g., 1 gram q 6 hours). In clinical studies, mortality rates of patients with bacteremic pneumococcal pneumonia and treated with β-lactam antibiotics were comparable for episodes caused by pneumococci susceptible and nonsusceptible to penicillin.[60]

Macrolide resistance is either due to modification of the target site, encoded by the *ermB* gene, or an active efflux pump that removes macrolides from the cell, encoded by the *mef* gene. In *S. pneumoniae*, the *erm* gene is associated with high levels of resistance to all macrolides. Erythromycin resistance based on efflux mechanisms can be overcome by the use of newer macrolides, such as azithromycin.[60]

The newer fluoroquinolones, such as levofloxacin and moxifloxacin, are active, *in vitro*, against most relevant significant aerobic Gram-positive cocci, the Enterobacteriaceae, *H. influenzae, M. catarrhalis, Legionella* species, *M. pneumoniae*, and *C. pneumoniae*, which make them attractive compounds for treatment of CAP. Development of resistance to fluoroquinolones, which can occur even during treatment, however, is a matter of serious concern.[61, 62] Resistance to fluoroquinolones results from mutations in the target enzymes (DNA gyrase and topoisomerase IV), thereby reducing the inhibitory effects of fluoroquinolones on bacterial DNA synthesis. Strains usually become fully resistant when both target genes are mutated. Other resistance mechanisms include alterations in the bacterial cell membrane and active efflux of the drug.[61, 62]

Importantly, prevalence of antibiotic resistance varies geographically. For instance, prevalence of reduced susceptibility to penicillin among *S. pneumoniae* is around 40% in Spain and $< 1\%$ in the Netherlands (http://www.earss.rivm.nl). Furthermore, over 50% of macrolide resistance in Europe is caused by mutations in the *ermB* gene,[63] whereas presence of an efflux pump is the predominant resistance mechanism of *S. pneumoniae* to macrolides in the United States.[60] Therefore, decisions on empirical antimicrobial treatment should be based on local antibiotic resistance rates.

Recently, an emergence of infections, mostly skin infection but sporadically severe CAP, caused by so-called community-associated methicillin-resistant *S. aureus* (CA-MRSA), have been reported from the United States and Europe.[64, 65] CA-MRSA are resistant to all β-lactam antibiotics, but are frequently still susceptible to clindamycin, co-trimoxazole, and fluoroquinolones.

## *Recommended Treatment*

When organisms are known, recommended treatment should be aimed at the isolated pathogen (Table 11.1). However, the initial treatment of CAP, as recommended in recent guidelines, is predominantly based on the clinical severity of presentation rather than the presumed causative pathogen (Table 11.2). For the prediction of clinical severity, several risk classifications exist which include combinations of underlying illnesses, age, and clinical features. In clinical practice, broad-spectrum antibiotics should be prescribed more liberally in patients

TABLE 11.1. Preferred pathogen-directed antimicrobial therapy for patients with community-acquired pneumonia, based on the recommendations for community-acquired pneumonia of the American Thoracic Society (ATS), British Thoracic Society (BTS), Infectious Diseases Society of America (IDSA), and the Dutch Working Party on Antibiotic Policy (SWAB)

| Microorganism | Preferred targeted therapy | Alternative antimicrobial therapy |
|---|---|---|
| *S. pneumoniae* | | |
| Penicillin susceptible, (MIC< 2 μg/ml) | • Penicillin G<br>• Amoxicillin | • Cephalosporin<br>• Macrolide<br>• Clindamycin<br>• Fluoroquinolone<br>• Doxycycline<br>• Carbapenem |
| Penicillin resistant | • Cefotaxime<br>• Ceftriaxone | • Fluoroquinolone<br>• Vancomycin |
| *H. influenzae* | • β-Lactam + β-lactamase inhibitor | • Cephalosporin (2nd or 3rd generation)<br>• Doxycycline<br>• Trimethoprim/sulfamethoxazole |
| *M. pneumoniae* | • Doxycycline<br>• Macrolide | • Fluoroquinolone |
| *C. pneumoniae* | • Doxycycline<br>• Macrolide | • Fluoroquinolone |
| *L. pneumophila* | • Macrolide ± rifampicin<br>• Fluoroquinolone | • Doxycycline ± rifampicin |
| *S. aureus* | | |
| Methicillin susceptible | • Flucloxacillin ± rifampin | • Cefazolin or cefuroxime<br>• Vancomycin<br>• Clindamycin<br>• Teicoplanin ± rifampicin<br>• Trimethoprim/sulfamethoxazole |
| Methicillin resistant | • Vancomycin ± rifampin or gentamicin | • Linezolid |
| *M. catarrhalis* | • Cephalosporin (2nd or 3rd generation)<br>• Trimethoprim/sulfamethoxazole<br>• Macrolide<br>• β-Lactam + β-lactamase inhibitor | • Fluoroquinolone |
| Anaerobes | • β-Lactam + β-lactamase inhibitor<br>• Clindamycin | • Imipenem |
| *P. aeruginosa* | • Aminoglycoside + antipseudomonal β-lactam (e.g., piperacillin)<br>• Carbapenem | • Aminoglycoside + ciprofloxacin<br>• Ciprofloxacin + antipseudomonal β-lactam |
| Enteric Gram-negative bacilli | • 3rd or 4th generation cephalosporin ± aminoglycoside<br>• Carbapenem | • β-Lactam + β-lactamase inhibitor<br>• Fluoroquinolone |
| *C. psittacci* | • Doxycycline | • Erythromycin<br>• Chloramphenicol |
| *Coxiella burnetii* | • Tetracycline | • Chloramphenicol |

TABLE 11.2. Preferred empirical therapy for community-acquired therapy (CAP) in lower respiratory tract infections, based on the recommendations for community-acquired pneumonia of the American Thoracic Society (ATS), British Thoracic Society (BTS), Infectious Diseases Society of America (IDSA), and the Dutch Working Party on Antibiotic Policy (SWAB)

| Severety of CAP | Recommended treatment in the USA (ATS and IDSA guidelines) | Recommended treatment in the UK (BTS guidelines) | Recommended treatment in the Netherlands (SWAB guidelines) |
|---|---|---|---|
| Mild infection (outpatients) | • Macrolide or doxycycline<br>• Fluoroquinolone | • Amoxicillin | • Amoxicillin<br>• doxycycline |
| Moderately severe infection (inpatients) | • Extended-spectrum cephalosporin plus macrolide<br>• β-Lactam/β-lactamase inhibitor plus macrolide<br>• Fluoroquinolone | • Amoxicillin + macrolide<br>*if mild infection, but admitted for other reasons than pneumonia, e.g., social situation or other condition*<br>• Amoxicillin | • Amoxicillin<br>• Penicillin<br>*If legionella urinary antigen test positive (performed within 12 h)*:<br>• Macrolide<br>• Quinolone |
| Severe infection (ICU treatment) | • Extended-spectrum cephalosporin plus macrolide<br>• β-Lactam/β-lactamase inhibitor plus either fluoroquinolone or macrolide<br>*Structural lung disease*<br>• Antipseudomonal agents<br>*Suspected aspiration*<br>• Fluoroquinolone ± clindamycin<br>• Metronidazole<br>• β-Lactam/β-lactamase inhibitor | • β-Lactam + β-lactamase inhibitor plus macrolide<br>• Cephalosporin (2nd/3rd generation) plus macrolide<br>• Fluoroquinolone with enhanced pneumococcal activity plus benzylpenicillin | • Moxifloxacin<br>• Penicillin + iprofloxacin<br>• β-Lactam + macrolide |

with "severe" CAP (SCAP). Therefore, a reliable prognostic model might be useful in tailoring empirical therapy in individual patients. Pragmatically, SCAP could be defined by the need of ICU admission. However, this definition does not include objective measurements and depends on local policies for ICU admission that may vary considerably between centers.[66] The ATS proposed to define SCAP on the presence of a certain set of minor and major clinical signs or symptoms.[50] The British Thoracic Society defined SCAP using a more or less similar set of "core," "additional," and "preexisting" adverse prognostic features.[67] Another algorithm to predict mortality risk and thus severity of CAP is the Pneumonia

Severity Index (PSI), which classifies patients in five groups. In the development of this scoring system, 30-day mortality rates gradually increased per class from 0.1% in class I, to 31.1% in class V.The ATS criteria had a high sensitivity but low specificity for predicting ICU admission[68] and in another study only 17% of patients in risk class V of the PSI system had been admitted to ICU.[69] To what extent these criteria and algorithms can be used for choosing empirical therapy remains to be determined.[50, 67, 69, 70] In our view, clinical judgment, which is difficult to describe in objective terms, remains important in the management of patients with CAP.

Results of nonexperimental studies have suggested that, in the initial management of patients hospitalized with CAP who do not require ICU admission, combination therapy consisting of a β-lactam antibiotic plus a macrolide or monotherapy with one of the newer fluoroquinolones reduces mortality and length of hospitalization.[71–78] Naturally, such strategies would increase the use of macrolides and fluoroquinolones and thus the selective antibiotic pressure for resistance.[79–81] The beneficial value of macrolides or fluoroquinolones might be the result of a larger than previously assumed role of atypical pathogens in the etiology of CAP, anti-inflammatory effects of macrolides, or resistance to β-lactams of the most important pathogens. However, the nonexperimental, and in almost all cases retrospective, design of these studies may have resulted in confounding by indication. Up till now, randomized controlled trials do not confirm these outcome differences.

The newer fluoroquinolones (levofloxacin and moxifloxacin) have been compared to β-lactam antibiotics (co-amoxiclav and ceftriaxone) with or without a macrolide in three randomized trials. Clinical and bacteriological success of fluoroquinolone treatment appeared to be better in two studies,[22, 82] and statistically significant differences in fever resolution and duration of hospitalization, in favor of fluoroquinolone treated patients, were also observed in two studies.[82, 83] Yet, the absolute differences were rather small (about 1 day for fever resolution and hospitalization), a significant survival benefit was not found, and results might have been influenced by protocol in at least one study, in which a switch to oral treatment for patients receiving ceftriaxone was not allowed before day 7.[83]

In adults with nonsevere CAP, treatment failures were comparable for empirical regimens with atypical coverage as compared to β-lactam antibiotics in meta-analysis.[84] A similar conclusion was reached in another meta-analysis of 24 trials, evaluating more than 5000 patients, treated for CAP. A trend toward increased clinical success and better bacteriological eradication was found for patients receiving atypical coverage, especially for those infected with *Legionella pneumophila*. Yet, this trend disappeared when only high-quality studies were evaluated.[85] Therefore, the recommendation to use empirical treatment with either a β-lactam/macrolide combination or monotherapy with a new fluoroquinolone for patients hospitalized with CAP is based on studies providing, at most, level III evidence.

### *Length of Treatment*

The recommended length of antimicrobial treatment of CAP is usually based on the causative pathogen, response to treatment, presence of comorbid illness, and complications. Current guidelines recommend to treat CAP caused by *S. pneumoniae* until the patient has been afebrile for 72 hours, whereas episodes caused by bacteria associated with pulmonary necrosis (e.g., *S. aureus, P. aeruginosa, Klebsiella*, and anaerobes) should be treated for about 2 weeks.[51] A duration of 2 weeks is also recommended for CAP caused by *M. pneumoniae, C. pneumoniae*, and legionnaires' disease in immunocompetent individuals. Treatment length could be reduced by using azithromycin, due to its long half-life in tissues, although longer courses are probably needed for *Legionella* infections.[51, 86]

These recommendations on treatment duration are not based on results of controlled trials. Recently, treatment durations of 3 and 8 days with amoxicillin ± clavulanic acid were compared in a randomized double-blind trial of 186 adult patients with mild CAP. At day 10, outcomes for clinical success, pathogen eradication, radiological response, and duration of hospitalization were similar for both groups, whereas adverse reactions occurred more frequently among patients receiving 8 days of amoxicillin.[87]

In conventional treatment approaches, intravenous therapy is continued until definite clinical cure has been achieved. Based on nonrandomized studies in patients with mild to moderately severe CAP, patients hospitalized with CAP can be managed safely and more efficiently by an early switch from IV to oral medication.[88–93] For patients with severe CAP, an early switch to oral antibiotic treatment also seems to reduce length of hospital stay (by approximately 2 days) and treatment associated costs, without adverse effects on treatment outcome.[94]

## Prevention

Prevention of CAP, for instance through vaccination, may well reduce antibiotic use and thus resistance development. With regard to respiratory infections, vaccines are available against pneumococci and influenza. Currently, a 23-valent pneumococcal polysaccharide vaccine (PPV), covering the 23 most prevalent serotypes of *S. pneumoniae*, is recommended in most Western countries for persons at high risk for developing CAP. However, the available data to support these recommendations are far from consistent. Nonexperimental retrospective studies suggest that PPV is effective and cost-saving in preventing invasive pneumococcal disease.[95, 96] However, confounding by indication might have played a considerable role in these studies affecting the validity of the results. Several clinical studies and systematic reviews yielded conflicting results with regard to the prevention of bacteremic pneumonia even in high-risk patients who were previously hospitalized with CAP.[96–102] Therefore, the

real value of pneumococcal vaccination strategies, in terms of effects on nonbacteremic pneumonia and costs, needs further exploration, preferably in randomized controlled trials.[103, 104]

Influenza vaccination is recommended for patients who have a high risk for influenza complications, like severe viral pneumonia or severe secondary bacterial infection. Patients at high risk for these complications can be identified based on host characteristics such as age, gender, comorbidity, and external factors, such as long-term immunosuppressive drug use or residence in closed communities with high transmission rates.[105] In meta-analysis vaccine effectiveness was 50% for preventing hospitalization and 68% for preventing death in high-risk patients. In addition to elderly patients, younger persons with high-risk medical conditions might also benefit from annual influenza vaccination.[101, 106, 107] Data on clinical effectiveness of the vaccine in reducing postinfluenza complications among high-risk persons of working age are limited and indicate no or at most limited benefits from vaccination.[102, 105, 108] Quantitative effects on antibiotic use of influenza vaccination are unknown, but it is tempting to argue that an effective influenza vaccination program might reduce antibiotic use.

## Conclusions

CAP is still among the most frequently encountered infections and accounts for considerable antibiotic consumption. Strategies to fight antibiotic resistance on a population level include several basic approaches: only treat when necessary, prescribe antibiotics for bacterial infections only, only treat causative pathogens, and reduce duration of treatment as much as possible. Physicians caring for CAP patients should balance these principles against the optimal treatment of the individual patient, which frequently includes broad-spectrum antibiotics as empirical therapy, especially in patients with severe CAP. As clinical features cannot adequately predict the causative microorganism, establishing an etiological diagnosis by means of urinary antigen tests or real-time PCR techinques may enhance streamlining of therapy, thereby reducing antibiotic pressure. Current guidelines advise broad spectrum antibiotics either with combinations of β-lactam antibiotics plus macrolides or monotherapy with fluoroquinolones for empirical treatment of severe CAP. Yet, different definitions are used for CAP severity and the recommendation of early broad-spectrum therapy is not supported by high-level evidence. The effects of these recommendations on resistance development are not clear, but should be a reason for concern.

More restrictive and prudent, but still responsible, use of antibiotics for CAP could possibly be achieved by improving techniques to establish etiological diagnoses, by optimizing empirical treatment through randomized trials, by optimizing duration of therapy, and implementation of vaccination strategies. However, these hypotheses remain to be proven.

## *References*


1. Marrie TJ. Community-acquired pneumonia. Clin Infect Dis 1994;18:501–513.
2. Chow AW, Hall CB, Klein JO, et al. General guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Clin Infect Dis 1992;15:s62–s88.
3. Koivula I, Sten M, Makela PH. Risk factors for pneumonia in the elderly. Am J Med 1994;96:313–320.
4. Lipsky BA, Boyko EJ, Inui TS, Koepsell TD. Risk factors for acquiring pneumococcal infections. Arch Intern Med 1986;146:2179–2185.
5. Roson B, Carratala J, Fernandez-Sabe N, et al. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. Arch Intern Med 2004;164:502–508.
6. Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French Study Group for Community-Acquired Pneumonia in the Intensive Care Unit. Chest 1994;105:1487–1495.
7. Torres A, Serra-Batlles J, Ferrer A, et al. Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis 1991;144:312–318.
8. Pinner RW, Teutsch SM, Simonsen L, et al. Trends in infectious diseases mortality in the United States. JAMA 1996;275:189–193.
9. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–186.
10. Pneumonia and influenza death rates—United States, 1979–1994. MMWR 1995;44:535–537.
11. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. JAMA 2005;294:2712–2719.
12. Oosterheert JJ, Bonten MJ, Hak E, et al. [The increase in pneumonia-related morbidity and mortality among adults in the Netherlands and possible explanations for it]. Ned Tijdschr Geneeskd 2004;148:1765–1769.
13. Guest JF, Morris A. Community-acquired pneumonia: The annual cost to the National Health Service in the UK. Eur Respir J 1997;10:1530–1534.
14. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 1997;157:1709–1718.
15. Lave JR, Lin CJ, Fine MJ, Hughes-Cromwick P. The cost of treating patients with community-acquired pneumonia. Semin Respir Crit Care Med 1999;20:189–197.
16. Ball P, Baquero F, Cars O, et al. Antibiotic therapy of community respiratory tract infections: Strategies for optimal outcomes and minimized resistance emergence. J Antimicrob Chemother 2002;49:31–40.
17. Ruiz M, Ewig S, Marcos MA, et al. Etiology of community acquired pneumonia: Impact of age, comorbidity and severity. Am J Respir Crit Care Med 1999;160:397–405.
18. Lim WS, Macfarlane JT, Boswell TCJ, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: Implications for management guidelines. Thorax 2001;56:296–301.

19. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: Influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis 2001;184:268–277.
20. Lieberman D, Schlaeffer F, Boldur I, et al. Multiple pathogens in adult patients admitted with community-acquired pneumonia: A one year prospective study of 346 consecutive patients. Thorax 1996;51:179–184.
21. Luna CM, Famiglietti A, Absi R, et al. Community-acquired pneumonia: Etiology, epidemiology, and outcome at a teaching hospital in Argentina. Chest 2000;118:1344–1354.
22. Finch R, Schurmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother 2002;46:1746–1754.
23. Bohte R, Furth R van, Broek PJ van den. Aetiology of community-acquired pneumonia; a prospective study among adults requiring admission to hospital. Thorax 1995;50:543–547.
24. Vegelin AL, Bissumbhar P, Joore JCA, Lammers JWJ, Hoepelman IM. Guidelines for severe community-acquired pneumonia in the western world. Neth J Med 1999;55:110–117.
25. van Elden LJ, van Loon AM, van Alphen F, et al. Frequent detection of human coronaviruses in clinical specimens from patients with respiratory tract infection by use of a novel real-time reverse-transcriptase polymerase chain reaction. J Infect Dis 2004;189:652–657.
26. Falsey AR, Walsh EE, Hayden FG. Rhinovirus and coronavirus infection-associated hospitalizations among older adults. J Infect Dis 2002;185:1338–1341.
27. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348:1967–1976.
28. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–1966.
29. Woo PC, Lau SK, Tsoi HW, et al. Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. Lancet 2004;363:841–845.
30. Vabret A, Mourez T, Gouarin S, Petitjean J, Freymuth F. An outbreak of coronavirus OC43 respiratory infection in Normandy, France. Clin Infect Dis 2003;36:985–989.
31. Hoek vdL, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med 2004;10:368–373.
32. Kahn JS. Human metapneumovirus: A newly emerging respiratory pathogen. Curr Opin Infect Dis 2003;16:255–258.
33. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–724.
34. Farr BM, Kaiser DL, Harrison BDW, Connolly CK. Prediction of microbial aetiology at admission to hospital for pneumonia from the presenting clinical features. Thorax 1989;44:1031–1035.
35. Macfarlane JT, Miller AC, Roderick Smith WH, Morris AH, Rose DH. Comparative radiographic features of community-acquired legionnaires' disease, pneumococcal pneumonia, mycoplasma pneumonia and psittacosis. Thorax 1984;39:28–33.

36. Woodhead MA, Macfarlane JT, American Thoracic Society. Comparative clinical and laboratory features of legionella with pneumococcal and mycoplasma pneumonias. Br J Dis Chest 1987;81:133–139.
37. Bohte R, Hermans J, van den Broek PJ. Early recognition of Streptococcus pneumoniae in patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 1996;15:201–205.
38. Hopstaken RM, Muris JW, Knottnerus JA, et al. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. Br J Gen Pract 2003;53:358–364.
39. Hopstaken RM, Stobberingh EE, Knottnerus JA, et al. Clinical items not helpful in differentiating viral from bacterial lower respiratory tract infections in general practice. J Clin Epidemiol 2005;58:175–183.
40. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004;113:701–707.
41. Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J 2000;19:598–602.
42. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: Cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600–607.
43. Waterer GW, Jennings SG, Wunderink RG. The impact of blood cultures on antibiotic therapy in pneumococcal pneumonia. Chest 1999;116:1278–1281.
44. Ewig S, Schlochtermeier M, Goke N, Niederman MS. Applying sputum as a diagnostic tool in pneumonia: Limited yield, minimal impact on treatment decisions. Chest 2002;121:1486–1492.
45. Reed WW, Byrd GS, Gates RH Jr, et al. Sputum Gram's stain in community acquired pneumonia: A meta analysis. West J Med 1996;165:197.
46. Smith PR. What diagnostic tests are needed for community-acquired pneumonia. Med Clin North Am 2001;85:1381–1396.
47. Corbo J, Friedman B, Bijur P, Gallagher EJ. Limited usefulness of initial blood cultures in community acquired pneumonia. Emerg Med J 2004;21:446–448.
48. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 2005;24:241–249.
49. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: A prospective randomised study. Thorax 2005;60:672–678.
50. American Thoracic Society. Guidelines for the management of adults with community acquired pneumonia. Am J Crit Care Med 2001;163:1730–1754.
51. Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis 2000;31:347–382.
52. Skov Sorensen UB, Henrichsen J. Cross-reactions between pneumococci and other streptococci due to C polysaccaride and F antigen. J Clin Microbiol 1987;25:1854–1859.

53. Murdoch DR, Laing RT, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine samples from adults with community-acquired pneumonia. Clin Microbiol 2001;39:3495–3498.
54. Dowell SF, Garman RL, Liu G, Levine OS, Yang YH. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. Clin Infect Dis 2001;32:824–825.
55. Yzerman EP, den Boer JW, Lettinga KD, et al. Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in the Netherlands. Clin Microbiol 2002;40:3232–3236.
56. Lettinga KD, Verbon A, Weverling GJ, et al. Legionnaires' disease at a Dutch flower show: Prognostic factors and impact of therapy. Emerg Infect Dis 2002;8:1448–1454.
57. Elden LJ van, Nijhuis M, Schipper P, Schuurman R, Loon AM van. Simultaneous detection of influenza viruses A and B using real-time quantitative PCR. Clin Microbiol 2001;39:196–200.
58. Oosterheert JJ, van Loon AM, Schuurman R, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. Clin Infect Dis 2005;41:1438–1444.
59. Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.
60. Garau J. Treatment of drug-resistant pneumococcal pneumonia. Lancet Infect Dis 2002;2:404–415.
61. Davidson R, Cavalcanti R, Brunton J, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. N Engl J Med 2002;346:747–749.
62. Low DE. Quinolone resistance among pneumococci: Therapeutic and diagnostic implications. Clin Infect Dis 2004;38 Suppl 4:S357-S362.
63. Johnston NJ, De Azavedo JC, Kellner JD, Low DE. Prevalence and characterization of the mechanisms of macrolide, lincosamide, and streptogramin resistance in isolates of Streptococcus pneumoniae. Antimicrob Agents Chemother 1998;42:2425–2426.
64. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005;352:1445–1453.
65. Bradley SF. Staphylococcus aureus pneumonia: Emergence of MRSA in the community. Semin Respir Crit Care Med 2005;26:643–649.
66. Neuhaus T, Ewig S. Defining severe community-acquired pneumonia. Med Clin North Am 2001;85:1413–1425.
67. BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 2001;56 Suppl 4:IV1–64.
68. Ewig S, Ruiz M, Mensa J, et al. Severe community-acquired pneumonia. Assessment of severity criteria. Am J Respir Crit Care Med 1998;158:1102–1108.
69. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community acquired pneumonia. N Engl J Med 1997;336:243–250.
70. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 2003;58:377–382.
71. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003;36:389–395.

72. Burgess DS, Lewis JS. Effect of macrolides as part of initial empiric therapy on medical outcomes for hospitalized patients with community-acquired pneumonia. Clin Ther 2000;22:872–878.
73. Dudas V, Hopefl A, Jacobs R, Guglielmo BJ. Antimicrobial selection for hospitalized patients with presumed community-acquired pneumonia: A survey of nonteaching US community hospitals. Ann Pharmacother 2000;34:446–452.
74. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. Arch Intern Med 1999;159:2562–2572.
75. Houck PM, MacLehose RF, Niederman MS, Lowery JK. Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states. Chest 2001;119:1420–1426.
76. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American city: A 20-year longitudinal study, 1978–1997. Am J Med 1999;107:34S-43S.
77. Stahl JE, Barza M, DesJardin J, Martin R, Eckman MH. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pnuemonia. Arch Intern Med 1999;159:2576–2580.
78. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe pneumococcal pneumonia. Arch Intern Med 2001;161:1837–1842.
79. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: Implications for fluoroquinolone use. JAMA 2003;289:885–888.
80. McCormick AW, Whitney CG, Farley MM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nat Med 2003;9:424–430.
81. Oosterheert JJ, Bonten MJ, Schneider MM, Hoepelman IM. Predicted effects on antibiotic use following the introduction of British or North American guidelines for community-acquired pneumonia in the Netherlands. Clin Microbiol Infect 2005;11:992–998.
82. File TM Jr, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 1997;41:1965–1972.
83. Welte T, Petermann W, Schurmann D, Bauer TT, Reimnitz P. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis 2005;41:1697–1705.
84. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005;330:456.
85. Shefet D, Robenshtok E, Paul M, Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: Systematic review of randomized controlled trials. Arch Intern Med 2005;165:1992–2000.
86. Matute AJ, Schurink CA, Hoepelman IM. Is a 5 day course of azithromycin enough for infections caused by Legionella pneumophila? J Antimicrob Chemother 2000;45:930–931.
87. El Moussaoui R., Prins J, et al. Three versus eight days of amoxicillin in mild to moderate-severe CAP. Program and Abstracts of the 44th Interscience Conference of Antimicrobial Agents and Chemotherapy 2004, Abstract L-661. Washington, DC.

88. Rhew DC, Weingarten SR. Achieving a safe and early discharge for patients with community-acquired pneumonia. Med Clin North Am 2001;85:1427–1440.
89. Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. Arch Intern Med 1995;155:1273–1276.
90. Ramirez JA, Vargas S, Ritter GW, et al. Early switch from intravenous to oral antibiotics and early hospital discharge: A prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Intern Med 1999;159:2449–2454.
91. Siegel RE, Halpern NA, Almenoff PL, et al. A prospective randomized study of inpatient iv. antibiotics for community-acquired pneumonia. The optimal duration of therapy. Chest 1996;110:965–971.
92. Siegel RE, Halpern NA, Almenoff PL, et al. A prospective randomized study of inpatient iv. antibiotics for community-acquired pneumonia. The optimal duration of therapy. Chest 1996;110:965–971.
93. Castro-Guardiola A, Viejo-Rodriguez AL, Soler-Simon S, et al. Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: A randomized controlled trial. Am J Med 2001;111:367–374.
94. Oosterheert JJ, Bonten MJ, Schneder MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in servere community acquired pneumonia: multicentre randomised trial. BMJ. 2006 Dec 9;333(7580):1193
95. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA 1997;278:1333–1339.
96. Ortqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. Lancet 1998;351:399–403.
97. Appelbaum PC. Resistance among Streptococcus pneumoniae: Implications for drug selection. Clin Infect Dis 2002;34:1613–1620.
98. Gross PA. Vaccines for pneumonia and new antiviral therapies. Med Clin North Am 2001;85:1531–1544.
99. Hak E, Grobbee DE, van Essen GA, Buskens E, Verheij TJ. Pneumococcal vaccination of the elderly: Do we need another trial? Arch Intern Med 2000;160:1698–1699.
100. Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999;159:2437–2442.
101. Christenson B, Lundbergh P, Hedlund J, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: A prospective study. Lancet 2001;357:1008–1011.
102. Ahmed F, Singleton JA, Franks AL. Clinical practice. Influenza vaccination for healthy young adults. N Engl J Med 2001;345:1543–1547.
103. Ament A, Fedson DS, Christie P. Pneumococcal vaccination and pneumonia: Even a low level of clinical effectiveness is highly cost-effective. Clin Infect Dis 2001;33:2079.
104. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: A study in 5 western European countries. Clin Infect Dis 2001;31:444–450.
105. Hak E, Hoes A, Verheij TJ. Influenza vaccination. Who needs them and when? Drugs 2002;62:2413–2420.

106. Hak E, Buskens E, van Essen GA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: The PRISMA study. Arch Intern Med 2005;165:274–280.
107. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med 1995;123:518–527.
108. Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. Vaccine 2000;18:957–1030.

*This page intentionally blank*

# Chapter 12
# Hospital-Acquired Pneumonia: Diagnostic and Treatment Options

María V. Torres, Patricia Muñoz, and Emilio Bouza

## Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide range of preventive measures (Craven et al. 1986, ATS 1996, Niederman 1996).

HAP is defined as pneumonia that occurs 48 hours or more after admission and that was not being incubated at the time of admission (Craven et al. 1986, Niederman 1996). HAP may be managed in a hospital ward or in the intensive care unit (ICU) when the illness is more severe. VAP is pneumonia that arises more than 48 hours after endotracheal intubation (Craven et al. 1986). Although not included in this definition, some patients may require intubation after developing severe HAP and should be managed in the same way as patients with VAP. Because most of the current data have been collected from patients with VAP, and microbiologic data from nonintubated patients may be less accurate, most of our information is from those with VAP, but by extrapolation can be applied to all patients with HAP.

## Epidemiology

HAP accounts for up to 25% of all ICU infections and for more than 50% of all antibiotics prescribed (Richards et al. 1999). VAP occurs in between 9% and 27% of all intubated patients (Chastre and Fagon 2002, Rello et al. 2002). In ICU patients, nearly 90% of the episodes of HAP occur during mechanical ventilation.

Time of onset of pneumonia is an important epidemiologic variable and a major risk factor for specific pathogens and different outcomes in patients with HAP and VAP. Early onset HAP and VAP, defined as occurring within the first 4–5 days of hospitalization, usually have a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria. Late-onset HAP and VAP (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity. However, patients

with early onset HAP who have received antibiotics or been hospitalized within the previous 90 days are at greater risk of colonization and infection with MDR pathogens and should be treated in the same way as patients with late-onset HAP or VAP (Trouillet et al. 1998).

The crude mortality rate for HAP may be as high as 30% to 70%, but many of these critically ill patients with HAP die of their underlying disease rather than of pneumonia. Mortality related to HAP—attributable mortality—has been estimated to be between 33% and 50% in several case-matching studies of VAP.

## Diagnosis

Diagnostic procedures are requested for two purposes: to define whether pneumonia is the explanation for a constellation of new signs and symptoms, and to determine the etiologic pathogen when pneumonia is present. Unfortunately, currently available tools cannot always reliably provide this information.

HAP is suspected if the patient has a radiographic infiltrate that is new or progressive and clinical findings suggesting infection (including new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation). When fever, leukocytosis, purulent sputum, and a positive culture of a sputum or tracheal aspirate are present without a new lung infiltrate, a diagnosis of nosocomial tracheobronchitis should be considered. The accuracy of the clinical diagnosis of VAP has been investigated using autopsy findings or quantitative cultures of either protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples as the standard for comparison. The presence of chest infiltrates, plus two of three clinical criteria (fever, purulent sputum, leukocytosis) resulted in 69% sensitivity and 75% specificity (Fabregas et al. 1999).

Although these criteria should lead us to suspect HAP or VAP, confirmation of the presence of pneumonia is much more difficult, and clinical parameters cannot be used to define the microbiologic etiology of pneumonia. The etiologic diagnosis generally requires a lower respiratory tract culture, but only rarely can it be made from blood or pleural fluid cultures. Respiratory tract cultures include endotracheal aspirates, BAL or PSB specimens. Overall, the sensitivity of blood cultures is less than 25%, and when positive, the organisms may frequently originate from an extrapulmonary source. Although an etiologic diagnosis is made from a respiratory tract culture, colonization of the trachea precedes development of pneumonia in almost all cases of VAP, and thus a positive culture cannot always distinguish a pathogen from a colonizing organism. However, a sterile culture from the lower respiratory tract of an intubated patient, in the absence of a recent change in antibiotic therapy, is strong evidence that bacterial pneumonia is not present, and an extrapulmonary site of infection should be considered (Souweine et al. 1998). In addition, the absence of MDR microorganisms from any lower respiratory specimen in intubated patients, with no change in antibiotics during the previous 72 hours, is strong evidence that they are not the causative pathogen.

In an effort to improve the specificity of clinical diagnosis of VAP, Pugin et al. developed the clinical pulmonary infection score (CPIS), which combines clinical, radiographic, physiological ($PaO_2/FIO_2$), and microbiologic data in a single numerical result (Pugin et al. 1991). When the CPIS was greater than 6, there was a good correlation with the presence of VAP (sensitivity of 77% and specificity of 42%).

### *Microbiological Diagnosis*

The bacteriologic strategy uses quantitative cultures of lower respiratory secretions (endotracheal aspirates, BAL or PSB specimens collected with or without a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to diagnose VAP/HAP and to determine the causative microorganism. Growth below the threshold is assumed to be due to colonization or contamination. Quantitative cultures have been shown to have good diagnostic utility for the presence of pneumonia, especially in patients with a low or equivocal clinical suspicion of infection (Heyland et al. 1999b). The diagnostic threshold varies with the technique used ($10^6$ cfu/ml for endotracheal aspirates, $10^4$–$10^5$ cfu/ml for bronchoscopic BAL, and $10^3$ cfu/ml for PSB samples). The choice of method depends on local expertise, experience, availability, and cost (Fagon et al. 2000a, Torres and Ewig 2004) Gram staining of polymorphonuclear leukocytes and macrophages and careful examination of the morphology of any bacteria found to be present may improve diagnostic accuracy when correlated with culture results (Chastre et al. 1995, Fartoukh et al. 2003). Conversely, a negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value for VAP (Blot et al. 2000). Pulmonary biopsy is a very invasive technique with a risk of pneumothorax and/or hemorrhaging, so it is not considered a first-line diagnostic test, even though it would avoid the possible contaminants of the upper airway. Complementary histopathology could be useful in those situations in which the causal agent is difficult to identify (Fabregas et al. 1996).

## General Approach to Antibiotic Treatment of HAP

The major goals for the management of HAP or VAP emphasize early administration of appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by deescalation of initial antibiotic therapy, based on microbiologic cultures and the clinical response of the patient, and shortening the duration of therapy to the minimum effective period. It is essential to recognize the variability of bacteriology from one hospital to another and from one time period to another, with the result that local microbiologic data should be taken into account when adapting treatment recommendations to a specific clinical setting. The initial, empiric antibiotic therapy algorithm includes two groups of patients: one with no need for

broad-spectrum therapy, with early onset pneumonia and no risk factors for MDR pathogens, and a second group that requires broad-spectrum therapy due to late-onset pneumonia or other risk factors for infection with MDR pathogens.

## Empiric Treatment of Ventilator-Associated Pneumonia

There are no specific global guidelines for the treatment of VAP and recommendations are based on the stratification of patients. Several studies have demonstrated that after 4–5 days in hospital, changes in patients' oropharyngeal flora may occur with acquisition of microorganisms typical of hospital settings. Other factors related to the host, previous antimicrobial treatment, and specific microorganisms existing in the ICU or hospital should also be considered. According to these factors, patients may be classified into the following two groups (Friedman et al. 2002).

**Group I:** patients without risk factors, and less than 5 days' hospitalization. Potential microorganisms are methicillin-sensitive *Staphylococcus aureus*, anaerobes, *Haemophilus influenzae, S.treptococcus pneumoniae*, and Enterobacteriaceae (*Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Proteus* spp., *Serratia marcescens*).

**Group II:** patients with risk factors or more than 5 days' hospitalization. The most likely microorganisms isolated would be those present in group I and resistant organisms such as *Pseudomonas aeruginosa, Acinetobacter* spp., *Citrobacter* spp., *Stenotrophomonas maltophilia*, or methicillin-resistant *S. aureus* (MRSA).

### *Empiric Treatment of Group I VAP*

The critical factor for changes in the expected flora is prior antimicrobial use (Alvarez-Lerma 1996, Luna et al. 1997, Kollef et al. 1999, Kollef 2000. The patients with the highest risk of developing VAP with endogenic flora are probably those with acute neurologic injuries such as head injury or cardiac arrest. There is a tendency for patients with head injury to be infected/colonized by *S. aureus*. The presence of MRSA needs to be considered in patients with recent hospitalizations or long-term institutionalization (Rello et al. 1992). Mortality from early onset VAP is about 24%. VAP also increases time on mechanical ventilation, ICU and hospital stay, morbidity, and, therefore, associated costs (Heyland et al. 1999).

Recommended therapy consists of monotherapy with ampicillin-sulbactam, levofloxacin, moxifloxacin, ciprofloxacin, ceftriaxone, or ertapenem. Combination therapy is not needed in this group of patients (Fink et al. 1994). The choice between these drugs is based on resistance patterns, especially among *S. pneumoniae*, *H. influenzae*, and *E. coli.* The increase in penicillin resistance in *S. pneumoniae* is well documented; however, the predominant use of quinolones for treatment of severe pneumonia is followed by emergence of resistance. Quinolones are recommended for patients with β-lactam allergy and, as alternatives, aztreonam or

glycopeptides, although empiric monotherapy with either of these two agents is not appropriate (Jones and Pfaller 2000).

### *Empiric Treatment of Group II VAP*

There is more consensus about this group of patients. Therapy should be with combinations, initiated early and subsequently adjusted to local microorganisms and microbiologic cultures. The most commonly recommended combination is a β-lactam with activity against *P. aeruginosa* (cefepime, cetazidime, piperacillin-tazobactam, or a carbapenem) plus a quinolone or an aminoglycoside. These drugs have good penetration into lung tissues and are safe. However, resistant isolates may appear during treatment especially when *P. aeruginosa* is involved. Therefore, patients at risk of *P. aeruginosa* infection (long-term hospitalization, prior antimicrobial treatment, chronic bronchopneumonia, age . 65 years, serum albumin , 2.5 g/dl) should receive combination therapy (Cometta et al. 1994). This broadens the antimicrobial spectrum, which is especially important considering that up to 55% of VAP have more than one causal organism. Another advantage of combined therapy is the synergistic effect in terms of efficacy and potential reduction of the emergence of resistance. On the other hand, combined therapy has a higher rate of side effects, toxicity, and costs (Leibovici et al. 1997, Combes et al. 2003, Neuhauser et al. 2003, Scheld 2003, West et al. 2003). Aminoglycosides, when indicated, achieve the greatest efficacy in VAP when administered in a single daily dose (Barza et al. 1996). Topical administration of antimicrobials such as colistin, aminoglycosides, or ceftazidime has been used prophylactically in patients with cystic fibrosis, although there are no data in VAP (Palmer et al. 1998).

Hospital units with a high prevalence of MRSA, especially if a β-lactam has been previously administered, must include a glycopeptide or linezolid in empiric therapy. Recent data show higher survival rates in patients receiving linezolid than in those receiving vancomycin (80 versus 64%) (Rubinstein et al. 2001, Wunderink et al. 2003b).

## Appropriate Antibiotic Selection and Adequate Dosing

Optimal outcome in patients with HAP or VAP can best be achieved with the combination of appropriate initial therapy and an adequate therapy regimen. To achieve adequate therapy, it is necessary to use not only the correct antibiotic, but also the optimal dose and the correct route of administration to ensure that the antibiotic reaches the site of infection. Combination therapy may be necessary (Fink et al. 1994).

Pharmacodynamic properties of specific antibiotics should be considered when selecting an adequate dosing regimen. For example, β-lactam antibiotics achieve less than 50% of their serum concentration in the lung, whereas fluoroquinolones and linezolid equal or exceed their serum concentration in bronchial secretion (ATS 1996, Conte et al. 2002).

The mechanism of action of certain agents can also affect dosing regimens, efficacy, and toxicity. Agents such as the aminoglycosides and quinolones are bactericidal depending on the concentration, their effect being faster at high concentrations. Other agents, such as vancomycin and the β–lactams, are also bactericidal, although their effect is more time-dependent (the effect is greater the longer the serum concentration is above the organism's minimal inhibitory concentration [MIC]). These pharmacodynamic effects lead to drug-specific dosing regimens.

All patients with HAP or VAP should initially receive therapy intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients (Paladino 1995).

## Local Instillation and Aerosolized Antibiotics

Local instillation or aerosolization can enhance antibiotic penetration to the lower respiratory tract. In the past, the agents most commonly administered and studied in this fashion have been the aminoglycosides and polymyxin B (Hamer 2000).

Aerosolized antibiotics may also be useful to treat microorganisms that, on the basis of high MIC values, are resistant to systemic therapy. Concern about aerosolized antibiotics leading to an increased risk of pneumonia due to resistant microorganisms was raised when these agents were used as prophylaxis, not as therapy. One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations.

In conclusion, aerosolized antibiotics have not been proven to have value in the therapy of VAP. However, they may be considered as adjunctive therapy in patients with MDR Gram-negative isolates who are not responding to systemic therapy (Hamer 2000).

## Combination versus Monotherapy

Combination therapy is common practice in suspected and proven Gram-negative HAP. The commonly cited reason for using combination therapy is to achieve synergy in the therapy of *P. aeruginosa*.

Combination regimens have also been recommended as a method to prevent the emergence of resistance during therapy, a common phenomenon when *P. aeruginosa* is treated with a variety of single agents and when *Enterobacter* spp. is treated with third-generation cephalosporins (Fink et al. 1994). Combination therapy should include agents from different classes to avoid antagonism of therapeutic mechanisms. For Gram-negatives, regimens usually involve the combination of two drugs (β-lactam, quinolone, or aminoglycoside). When combination therapy includes an aminoglycoside-containing regimen, the aminoglycoside can be stopped after 5–7 days in responding patients (Gruson et al. 2000).

Monotherapy should be used when possible, because combination therapy is often expensive and exposes patients to unnecessary antibiotics, thereby increasing the risk of MDR pathogens and adverse outcome. Patients who develop nosocomial pneumonia with no risk factors for drug-resistant organisms are likely to respond to monotherapy. Monotherapy is also the standard when Gram-positive HAP or VAP, including MRSA, is documented.

## Full-Length Treatment for VAP

Individual factors influence the length of therapy depending on the severity of the VAP episode, etiology, and clinical response. Therefore, a patient with favorable clinical evolution and an endogenous causal microorganism may be treated for 7 to 10 days as recommended by the American Thoracic Society (ATS). In contrast, multiresistant microorganisms (especially nonfermenting Gram-negatives) should receive at least 14 days' therapy (Guidelines 2005). In all cases, clinical parameters such as defervescence of fever, decrease in white blood cell count, improvement in gas exchange, and subsequent negative cultures (reliable indicators of a good clinical outcome) are essential when deciding to end antimicrobial treatment. Appropriate treatment may restore clinical parameters to normal after 1 week. Overuse of antimicrobials does not seem reasonable, since it may increase side effects, risk of toxicity, emergence of MDR microorganisms, and cost of the episode.

## Special Situations

The clinical or therapeutic characteristics of some VAP groups mean that they require special attention, as follows.

### *1. P. aeruginosa*

*P. aeruginosa* has the capacity to develop resistance to all known classes of antibiotics, and resistance has been observed in between 30% and 50% of patients currently receiving monotherapy. However, no data show that this problem can be avoided by the use of combination therapy (Fink et al. 1994). Although combination therapy will not necessarily prevent the development of resistance, it is less likely to lead to inappropriate and ineffective treatment (Ibrahim et al. 2001). Cross-infection is also a serious problem, and the antibiotics given to adjacent patients may affect the risk for infection with an MDR strain. All of the studies of combination therapy have used an aminoglycoside with a β-lactam. In these cases, the aminoglycoside can be stopped after 5–7 days in responding patients (Gruson et al. 2000). A quinolone could be an alternative to an aminoglycoside, with the theoretical advantage of improved respiratory tract penetration and less nephrotoxicity. If a quinolone is used in combination therapy for *P. aeruginosa*, ciprofloxacin

or levofloxacin may be chosen on the basis of in vitro activity, but should only be used if local susceptibility data show activity of these agents and at higher doses. This remains a problem, because a significant fall in *P. aeruginosa* sensitivity to quinolones has resulted from widespread use of these agents in hospitals (Neuhauser et al. 2003, Scheld 2003). As mentioned, some anecdotal experience has suggested the value of aerosolized antibiotics as an adjunct to systemic therapy in patients with highly resistant *P. aeruginosa* pneumonia (Hamer 2000).

## *2. Acinetobacter spp.*

The antibiotic armamentarium for the treatment of *Acinetobacter* spp. is limited because of native resistance to many classes of antibiotics. The most consistently effective antibiotics are the carbapenems, the sulbactam component of ampicillin-sulbactam, and the polymyxins. The emergence of carbapenem-resistant clones suggests that optimal doses of carbapenems should be used. The significant nephrotoxicity of the polymyxins limits widespread intravenous use, but there are reports of efficacy with acceptable toxicity, and these agents can also be used as aerosolized therapy (Hamer 2000, Garnacho-Montero et al. 2003). Susceptibility to aminoglycosides is variable and poor penetration may limit the delivery of adequate tissue levels of antibiotics, suggesting a possible role for aerosol delivery of these agents for selected patients with *Acinetobacter* pneumonia. One report has documented the efficacy and safety of colistin in patients with *Acinetobacter* VAP that was not susceptible to carbapenems (Garnacho-Montero et al. 2003). Colistin therapy led to a clinical cure in 57% of patients, and none had prolonged neuromuscular blockade as a side effect of therapy.

## *3. Extended-Spectrum β–Lactamase-Producing (ESBL)* Enterobacteriaceae

The hallmark of ESBL Enterobacteriaceae is a variable response to cephalosporins and thus third-generation agents should be avoided as therapy when these pathogens are suspected or isolated (Paterson et al. 2001). In particular, a third-generation cephalosporin should not be used for *Enterobacter* spp. because of the documented high frequency of resistance developing on therapy (Chow et al. 1991). Carbapenems provide a reliable choice, as they are generally active against these organisms (Paterson et al. 2004). Because these microorganisms are also likely to show resistance to aminoglycosides and fluoroquinolones, the benefit of combination therapy is uncertain. Piperacillin-tazobactam has been used for the treatment of VAP, but its efficacy against ESBL organisms is uncertain and it should be used with caution (Fowler et al. 2003).

## *4. Methicillin-Resistant Staphylococcus aureus (MRSA)*

Although vancomycin has been the accepted standard of therapy for this pathogen, clinical trials have consistently reported clinical failures rates of

40% or greater with a standard dose (1 g every 12 hours) of vancomycin (Malangoni et al. 1994, Fagon et al. 2000). Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and may be preferred. Linezolid has shown a significant association with both improved clinical cure and lower mortality (Wunderink et al. 2003a). This advantage may be due to the higher penetration of linezolid into the epithelial lining fluid than with vancomycin (Conte et al. 2002). Linezolid may also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents, particularly aminoglycosides, because the presence of renal insufficiency is a significant predictor of vancomycin failure (Goetz and Sayers 1993).

## Antibiotic Heterogeneity and Antibiotic Cycling

Antibiotic cycling or rotation has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance (Kollef 2001). In theory, a class of antibiotics or a specific antibiotic is withdrawn from use for a defined time period and later reintroduced in an attempt to limit bacterial resistance to the cycled antimicrobial agents.

Outbreaks of infection by a specific strain of resistant bacteria can be successfully managed by restricted access to specific antibiotics, generally with no impact on the overall frequency of resistance (Rahal et al. 1998). However, if disproportionate use of another antibiotic is a consequence, resistance rates may be affected.

In conclusion, although heterogeneity of antibiotic prescriptions may enable us to reduce the overall frequency of antibiotic resistance, the long-term impact of this practice is unknown (Kollef et al. 2000, Gruson et al. 2003).

## Response to Therapy

### *Modification of Empiric Antibiotic Regimens*

Empiric antibiotics may need modification once the results of blood or respiratory tract cultures become available, and empiric therapy may need to be modified. Modification may be necessary if a resistant or unsuspected pathogen is found in a nonresponding patient. Alternatively, therapy can be deescalated or narrowed if an anticipated organism (such as *P. aeruginosa* or *Acinetobacter* spp.) is not recovered or if the organism isolated is sensitive to a less broad-spectrum antibiotic than was used in the initial regimen.

### *Defining the Normal Pattern of Resolution*

Resolution of HAP or VAP can be defined either clinically or microbiologically. Clinical end points such as improvement, resolution, delayed resolution, relapse,

failure, and death can be defined (Luna and Niederman 2002). Using this approach, clinical improvement usually becomes apparent after the first 48–72 hours of therapy and, therefore, the selected antimicrobial regimen should not be changed during this time unless progressive deterioration is noted (Luna and Niederman 2002, Luna et al. 2003).

Appropriate respiratory tract cultures can be used to define microbiologic resolution. Serial cultures allow us to define end points, such as bacterial eradication, superinfections (infection with a new organism), recurrent infection (elimination followed by return of the original organism), or microbiologic persistence. Serial quantitative microbiologic studies of lower respiratory tract secretions can also define the resolution end point (Dennesen et al. 2001).

Chest radiographs are of limited value for defining clinical improvement in severe pneumonia, and initial radiographic deterioration is common, especially among patients with bacteremia or who are infected with highly virulent organisms. In addition, radiographic improvement often lags behind clinical parameters, especially in the elderly and in individuals with coexisting disease (e.g., chronic obstructive pulmonary disease) (Luna et al. 2003). However, the finding of a rapidly deteriorating radiographic pattern, with a follow-up chest radiograph showing progression to multilobar involvement, a greater than 50% increase in the size of the infiltrate within 48 hours, development of cavitary disease, or significant pleural effusion, should raise concern (ATS 1996).

Clinical parameters including white blood cell count and measures of oxygenation and core temperature have been used in several studies to define the normal pattern of resolution of HAP.

## *Reasons for Deterioration or Nonresolution*

There are several possible causes of rapid deterioration or failure to improve. These include the possibility that the process being treated is not pneumonia or that certain host, bacterial, and therapeutic factors have not been considered.

Many noninfectious processes may be mistaken for HAP, including atelectasis, congestive heart failure, pulmonary embolus with infarction, lung contusion, and chemical pneumonitis after aspiration (Wunderink et al. 1992).

Host factors associated with a failure to improve during empiric therapy include the presence of any condition that is known to increase mortality, e.g., prolonged mechanical ventilation, respiratory failure, an underlying fatal condition, age greater than 60 years, bilateral radiographic infiltrates, prior antibiotic therapy, prior pneumonia, and/or chronic lung disease (Torres et al. 1990, Luna and Niederman 2002).

Bacterial variables can also be associated with an adverse outcome of initial therapy. The infecting pathogen can be resistant at the outset to the chosen antibiotic or can acquire resistance during therapy, particularly *P. aeruginosa* treated with a single agent (Fink et al. 1994). Certain types of infection are associated with a poor outcome, especially those with Gram-negative bacilli, polymicrobial flora, or bacteria that have acquired antibiotic resistance (Fagon et al. 1993,

Luna et al. 1999). In patients who are mechanically ventilated, superinfection with *P. aeruginosa* or *Acinetobacter* spp. has a particularly high mortality. Finally, pneumonia can be due to other pathogens (i.e., *Mycobacterium tuberculosis*, fungi, or respiratory viruses) or an unusual bacterial pathogen not included in the initial empiric regimen. In addition, some patients can have clinically unrecognized immunosuppression and *Pneumocystis jiroveci* or *Aspergillus* spp. pneumonia may be a cause of nonresponse to therapy.

Certain complications during therapy can also lead to an apparent failure in response to therapy. Some patients with HAP or VAP can have other sources of fever simultaneously, particularly sinusitis, vascular catheter-related infection, pseudomembranous enterocolitis, or urinary tract infections (Meduri et al. 1994). Complications of the original pneumonia can also lead to failure, including development of lung abscess or empyema. Other possible causes of persistent fever or pulmonary infiltrates include drug fever, sepsis with multiple system organ failure, or pulmonary embolus with secondary infarction.

## *Evaluation of the Nonresponding Patient*

For patients who are deteriorating rapidly or not responding to initial therapy, it may be necessary to broaden antimicrobial coverage while awaiting the results of culture and other diagnostic studies. A detailed evaluation is required, with a careful differential diagnosis and a repeat sampling of lower respiratory tract secretions for culture and antimicrobial sensitivity patterns. Even though patients in this clinical setting are receiving antibiotics, recovery by invasive methods is possible and may indicate that infection with a resistant organism is present (Souweine et al. 1998). If cultures do show a resistant or unusual pathogen, therapy can be modified appropriately. If cultures do not show a resistant or unsuspected pathogen, then consideration of a noninfectious process or one of the complicating problems is appropriate. This necessitates the changing of vascular access catheters and the culture of blood, catheter tips that have been removed, and urine, as well as other accessible sites.

Specialized radiological procedures may be helpful in identifying anatomic reasons for failure. Lateral decubitus chest radiographs, ultrasound, or computed tomography (CT) may reveal pleural fluid, which should be evaluated to exclude empyema. In addition, CT scanning can distinguish between pleural fluid and parenchymal disease, and can reveal parenchymal abscesses, adenopathies, and pulmonary masses. CT scanning of extrathoracic sites may also help to identify other areas of infection, and particular attention should be focused on the abdomen in patients who have adult respiratory distress syndrome (ARDS).

If this microbiologic and radiographic evaluation is negative, a decision should be made concerning whether to observe the patient while either continuing or empirically changing antibiotics or to perform an open lung biopsy.

If the patient remains hemodynamically stable but does not show evidence of clinical improvement, and bronchoscopic and radiologic evaluations are unrevealing, switching antibiotics or initiating anti-inflammatory therapy (corticosteroids)

may be appropriate before proceeding with an open biopsy. However, if the patient deteriorates early (within the first 48–72 hours of therapy) or has initially improved but then deteriorates, additional antibiotics directed at resistant or unusual bacteria can be added while carrying out specialized radiological procedures and microbiologic evaluations.

## *References*

Alvarez-Lerma F (1996) Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 22:387–394.

American Thoracic Society, November 1995 (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies. A consensus statement. Am J Respir Crit Care Med 153:1711–1725.

Barza M, et al (1996) Single or multiple daily doses of aminoglycosides: A meta-analysis. BMJ 312:338–345.

Blot F, et al (2000) Value of Gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 162:1731–1737.

Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903.

Chastre J, et al (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 152:231–240.

Chow JW, et al (1991) *Enterobacter* bacteremia: Clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med 115:585–590.

Combes A, et al (2003) Factors predicting ventilator-associated pneumonia recurrence. Crit Care Med 31:1102–1107.

Cometta A, et al (1994) Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob Agents Chemother 38:1309–1313.

Conte JE Jr, et al (2002) Intrapulmonary pharmacokinetics of linezolid. Antimicrob Agents Chemother 46:1475–1480.

Craven DE, et al (1986) Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 133:792–796.

Dennesen PJ, et al (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375.

Fabregas N, et al (1996) Histopathologic and microbiologic aspects of ventilator-associated pneumonia. Anesthesiology 84:760–771.

Fabregas N, et al (1999) Clinical diagnosis of ventilator associated pneumonia revisited: Comparative validation using immediate post-mortem lung biopsies. Thorax 54:867–873.

Fagon JY, et al (1993) Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. Am J Med 94:281–288.

Fagon JY, et al (2000a) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med 132:621–630.

Fagon JY, et al (2000b) Treatment of gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med 161:753–762.

Fartoukh M, et al (2003) Diagnosing pneumonia during mechanical ventilation: The clinical pulmonary infection score revisited. Am J Respir Crit Care Med 168:173–179.

Fink MP, et al (1994) Treatment of severe pneumonia in hospitalized patients: Results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group. Antimicrob Agents Chemother 38:547–557.

Fowler RA, et al (2003) Variability in antibiotic prescribing patterns and outcomes in patients with clinically suspected ventilator-associated pneumonia. Chest 123:835–844.

Friedman ND, et al (2002) Health-care-associated bloodstream infections in adults: A reason to change the accepted definition of community-acquired infections. Ann Intern Med 137:791–797.

Garnacho-Montero J, et al (2003) Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. Clin Infect Dis 36:1111–1118.

Goetz MB, Sayers J (1993) Nephrotoxicity of vancomycin and aminoglycoside therapy separately and in combination. J Antimicrob Chemother 32:325–334.

Gruson D, et al (2000) Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am J Respir Crit Care Med 162:837–843.

Gruson D, et al (2003) Strategy of antibiotic rotation: Long-term effect on incidence and susceptibilities of Gram-negative bacilli responsible for ventilator-associated pneumonia. Crit Care Med 31:1908–1914.

Guidelines (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416.

Hamer DH (2000) Treatment of nosocomial pneumonia and tracheobronchitis caused by multidrug-resistant *Pseudomonas aeruginosa* with aerosolized colistin. Am J Respir Crit Care Med 162:328–330.

Heyland DK, et al (1999a) The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 159:1249–1256.

Heyland DK, et al (1999b) The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Canadian Critical Care Trials Group. Chest 115:1076–1084.

Ibrahim EH, et al (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 29:1109–1115.

Jones RN, Pfaller MA (2000) In vitro activity of newer fluoroquinolones for respiratory tract infections and emerging patterns of antimicrobial resistance: Data from the SENTRY antimicrobial surveillance program. Clin Infect Dis 31 Suppl 2:S16–23.

Kollef MH (2000) Inadequate antimicrobial treatment: An important determinant of outcome for hospitalized patients. Clin Infect Dis 31:S131–138.

Kollef MH (2001) Is there a role for antibiotic cycling in the intensive care unit? Crit Care Med 29:N135–142.

Kollef MH, et al (1999) Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. Chest 115:462–474.

Kollef MH, et al (2000) Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. Crit Care Med 28:3456–3464.

Leibovici L, et al (1997) Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: A prospective, observational study. Antimicrob Agents Chemother 41:1127–1133.

Luna CM, Niederman MS (2002) What is the natural history of resolution of nosocomial pneumonia? Semin Respir Crit Care Med 23:471–479.
Luna CM, et al (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 111:676–685.
Luna CM, et al (1999) Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. Chest 116:1075–1084.
Luna CM, et al (2003) Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 31:676–682.
Malangoni MA, et al (1994) Pneumonia in the surgical intensive care unit: Factors determining successful outcome. Am J Surg 167:250–255.
Meduri GU, et al (1994) Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest 106:221–235.
Neuhauser MM, et al (2003) Antibiotic resistance among gram-negative bacilli in US intensive care units: Implications for fluoroquinolone use. JAMA 289:885–888.
Niederman MS (1996) Guidelines for the management of respiratory infection: Why do we need them, how should they be developed, and can they be useful? Curr Opin Pulm Med 2:161–165.
Paladino JA (1995) Pharmacoeconomic comparison of sequential IV/oral ciprofloxacin versus ceftazidime in the treatment of nosocomial pneumonia. Can J Hosp Pharm 48:276–283.
Palmer LB, et al (1998) Aerosolized antibiotics in mechanically ventilated patients: Delivery and response. Crit Care Med 26:31–39.
Paterson DL, et al (2001) Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum beta-lactamases: Implications for the clinical microbiology laboratory. J Clin Microbiol 39: 2206–2212.
Paterson DL, et al (2004) Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: Implications of production of extended-spectrum beta-lactamases. Clin Infect Dis 39:31–37.
Pugin J, et al (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 143:1121–1129.
Rahal JJ, et al (1998) Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial *Klebsiella*. JAMA 280:1233–1237.
Rello J, et al (1992) Nosocomial pneumonia in critically ill comatose patients: Need for a differential therapeutic approach. Eur Respir J 5:1249–1253.
Rello J, et al (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 122:2115–2121.
Richards MJ, et al (1999) Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 27:887–892.
Rubinstein E, et al (2001) Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: A randomized, double-blind, multicenter study. Clin Infect Dis 32:402–412.
Scheld WM (2003) Maintaining fluoroquinolone class efficacy: Review of influencing factors. Emerg Infect Dis 9:1–9.
Souweine B, et al (1998) Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: Impact of previous antimicrobial treatments. Crit Care Med 26:236–244.

Torres A, Ewig S (2004) Diagnosing ventilator-associated pneumonia. N Engl J Med 350:433–435.

Torres A, et al (1990) Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 142:523–528.

Trouillet JL, et al (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157:531–539.

West M, et al (2003) Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: A multicenter, prospective, randomized, open-label study. Clin Ther 25:485–506.

Wunderink RG, et al (1992) The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. Chest 101:458–463.

Wunderink RG, et al (2003a) Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther 25:980–992.

Wunderink RG, et al (2003b) Linezolid vs vancomycin: Analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest 124:1789–1797.

*This page intentionally blank*

# Chapter 13
# Optimizing Antimicrobial Chemotherapy in the ICU—A Review

Ian M. Gould

## Abstract

Infection is a common cause of admission to the ICU and is also commonly acquired on the ICU. Appropriate, early treatment improves outcome but choice of therapy is often empiric because of the delay in processing most microbiological specimens. This encourages the use of broad spectrum agents which leads to the selection of multiresistant bacteria, setting up a vicious circle of antibiotic use and resistance. The problem is enhanced by poor adherence to infection control procedures and the most intensive use of antibiotics anywhere in the hospital. Current resistant problems are greater than ever experienced and herald the dawn of untreatable infections. This comes during a period of reduced pharmaceutical company research on developing new agents. The author reviews the various strategies that can be employed to improve the quality of antibiotic prescribing in order to both improve patient outcome and reduce the selection of resistant strains. The use of the microbiological laboratory is explored in particular detail as are new pharmacodynamic concepts which guide dosing schedules. Particular attention is paid to combination therapy, stewardship strategies, and empiric treatment choices.

## Introduction

The typical intensive care unit (ICU) is ideal for the selection, maintenance, and spread of multiresistant organisms. This is due to a complex mix of factors including a very susceptible patient population, many cross infection opportunities, and high-level use of antibiotics. These factors make the selection of appropriate antibiotic therapy even more critical than in any other areas of the hospital, not only to ensure that heavily immunosuppressed, critically ill patients receive highly active, usually empiric treatment in the correct dose as soon as possible but also because every prescription on the ICU adds to the selective pressure for even more resistant phenotypes.

In this review I will describe these issues as they pertain to the treatment of infection on the ICU and consider in detail the decision making processes and strategies to be employed, both in treating individual patients and also in development of an overall antibiotic prescribing policy for the ICU.

## Trends in Sepsis and Mortality

Over the past two decades there has been an overall increase in severe infection associated with the sepsis syndrome although mortality has leveled off at around 25%.[1] Similarly, the microbes causing this syndrome, usually Gram positive or Gram negative bacteria, have ceased to increase in numbers in the last few years, to be joined by an increasing number of fungal infections.

Within Europe, mortality rates in ICUs are closely related to infection rates by country[2] although there are some outliers such as the United Kingdom with relatively high mortality. This raises the important issue of what exactly authors mean by an ICU. It is evident that there are relatively fewer ICU beds in the United Kingdom than in many other European countries. Clearly the intensity of care within U.K. ICU beds is much higher than in many comparable countries. In the United Kingdom one is unlikely to be admitted to an ICU unless requiring ventilation whereas some other countries include postoperative, high dependency, and even coronary care beds in their definition of ICU beds.

## Differences in Susceptibility to Infection and Types of Infection

Clearly ICU patients are very susceptible to infection, not only because of underlying illnesses but also because many diagnostic and therapeutic procedures are immunosuppressive. In addition, the types of infection seen in ICU patients can differ significantly from those in other parts of the hospital with pneumonia and bacteremia predominating.[3] The reasons for this are often iatrogenic with ventilation and intravascular access predisposing to these infections.[4] In addition, life-threatening community- or hospital-acquired infection can be the reason for admission to the ICU.

## Multiresistant Infections

It is well established that ICUs tend to harbor a more resistant collection of infections than elsewhere in the hospital and the reasons for this are complex.[5, 6] Many of the patients on the ICU have prior prolonged hospital stay, immunosuppression, and antibiotic exposure, all of which will predispose to carriage of multiresistant organisms on admission to the ICU.[7] Once there they are often subjected to further intensive use of antibiotic and poor adherence to control of infection procedures. These will select for and spread further resistance, often in the form of multiresistant clones that colonize other patients, staff, and the environment of the ICU including items of equipment such as ventilators.[8, 9] Such epidemic or indeed endemic organisms frequently include

methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), Acinetobacter spp, and extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL).[10–13] The epidemiology and control of such multiresistant organisms has been the subject of many previous publications and is not within the scope of this review. Suffice to say, they continue to plague many ICUs causing major problems.

Another area that has not received much attention but that is crucial to the control of these multiresistant strains is the intensity of antibiotic use in ICUs. This can be severalfold higher than hospital use as a whole with 200–400 defined daily doses (DDD) per 100 occupied bed days not uncommon.[14, 15] Not only is total antibiotic use intense, but the ICU is likely to be the highest user of the newest, broad-spectrum agents and double and triple antibiotic combinations are often the norm in such patients. A vicious circle of increasing resistance necessitating the prescription of ever more broad spectrum drugs perpetuates the problem until untreatable infections become a real prospect.

## Trends in Antibiotic Susceptibility of ICU Pathogens

The net result is that resistant problems in the ICU are worse than in the rest of the hospital and show signs of further deterioration in the last few years. As well as the epidemic clones previously mentioned, which are now the norm in many European ICUs, carbapenem resistance is also increasingly common. In Pseudomonas aeruginosa resistance is commonly due to reduced permeability to or increased efflux of antibiotic, but more worryingly, in Acinetobacter baumannii and Enterobacteriaceae it is usually due to plasmid-mediated carbapenemases.[16, 17] Derepressed and inducible AmpC β-lactamase-producing Enterobacteria with resistance to most cephalosporins are also the norm, at least in the United Kingdom and southern Europe. Aminoglycoside resistance is, perhaps, less of a problem although increasing in some units.[18]

## Principles of Antibiotic Treatment

### *The Importance of Early Treatment*

It is now well established that appropriate antimicrobial treatment (as judged by *in vitro* susceptibility testing) improves survival[19] and a recent paper shows the importance of this being given as early as possible in the infection process.[20] Thirty day mortality increased from 27.7% to 54.8% when the delay in appropriate treatment extended from $<24$ h to $>120$ h.

There are persuasive theoretical reasons why this should be the case. Clinically of course, treatment before the onset of the sepsis syndrome and avoidance of

organ failure improves survival. Microbiologically, early treatment has several benefits because of a lower inoculum of bacteria at the infection site. This ensures greater susceptibility to the antibiotic, due to the inoculum effect,[21] less chance of selecting resistant mutants,[22] and less chance of abscess formation which will often need drainage.

In the laboratory, when performing in vitro susceptibility tests, a standardized inoculum of $10^5$ bacteria/ml of culture broth is used to test susceptibility. In an abscess or severe pneumonia there are likely to be $.10^8$ bacteria/ml of pus or sputum. Cephalosporin and penicillin antibiotics, in particular, are susceptible to the inoculum effect. This is usually because of the production of β–lactamase enzymes which, if present at the high concentrations seen in a high inoculum infection, can significantly alter the susceptibility of the bacteria. Other causes of the inoculum effect may be reduced metabolic activity of higher concentrations of bacteria and the production of biofilm.[23] Thus, in the standard laboratory susceptibility test, the activity of an antibiotic can be significantly overestimated.

Numbers of bacteria are important also in the development of resistance in a patient. Many bacteria will have natural mutation rates with emergence of resistant isolates in around one in every $10^{6–8}$ divisions.[22] The presence of certain antibiotics or clinical conditions may increase these mutation rates.[24] Again it can be seen that the higher the bacterial inoculum, the more likely is a resistant mutant to occur or preexist and multiply under the selective pressure of treatment, perhaps causing treatment failure or relapse.

## The Pharmacodynamics of Antibiotic Treatment

Antibiotics can traditionally be categorized according to their mode of action into those that are bactericidal and those that are bacteriostatic. Often this may be an artificial division (see inoculum effect previously) but there is some reasonable evidence that effective bactericidal action can actually make a difference by reducing the selection of resistant mutants.[25] At the same time, rapid bactericidal action can cause endotoxin release with well known consequences, for instance in syphilis and meningococcal infections.[26] On balance, however, it is often considered best to achieve as rapid a bactericidal activity as possible to reduce bacterial load. This may be problematic in critical patients if treated with low-dose β-lactams, in particular cephalosporins that bind preferentially to penicillin binding protein 3 at low concentrations.[21] Monotherapy with such agents can lead to filament formation and buildup of endotoxins which, if then subjected to higher, bactericidal concentrations of antibiotic can lead to rapid cell death and release of large levels of free endotoxin. The clinical consequences of this are still debated despite the ability of these filaments to reach many times the length of the parent bacteria due to inability to form cell cross-walls. It does, however, seem prudent to avoid undertreatment by monotherapy with such agents.

The other common way to classify antibiotics according to their mode of action, is time dependent or concentration dependent and this probably has more far-reaching consequences in terms of dosing schedules.[27,28] The classical time-dependent antibiotics are the β-lactams and outcome here is dependent on a prolonged concentration, at the site of infection, above the minimum inhibitory concentration (MIC) of the organism being treated (T>. MIC). In fact, while for immunocompetent animals, T>. MIC of 50% of the dosing interval is probably satisfactory for optimal outcome, for seriously ill, immunocompromised patients such as those commonly found on any ICU, then T>. 4–8 × MIC for 100% of the dosing interval should be aimed for.[29] This will prevent the selection of resistant mutants and take advantage of any concentration dependent bacterial killing, particularly likely with the carbapenems.[30] For this reason, continuous infusion β–lactam therapy is sometimes used in ICUs.[31]

The classical concentration-dependent antibiotics are the quinolones and aminoglycosides. Their bactericidal effect is markedly improved at concentrations many times above the MIC. For aminoglycosides this fits in conveniently with the benefits of a single daily dose for avoiding nephro- and oto-toxicity.[32] High peak concentrations may also prevent selection of resistant mutants, a concept thought particularly relevant for the quinolone antibiotics.[33] For such concentration dependent drugs, it should not matter if concentrations at the site of infection fall below the MIC for periods of several hours due to their prolonged suppressive effects on growth and sub-MIC effects, but this is probably more a safety valve and should not be factored into dosing schedules.[34] Simply put, with concentration-dependent antibiotics, the more antibiotic that is administered the better, with the obvious caveats of toxicity and cost. Outcome can often be shown to be most closely related to the area under the curve (AUC) MIC ratio with ratios >125 being considered optimal.[29]

## Combination Therapy

Combination therapy has been popular for many years in the treatment of serious infections and has several potential benefits. Most commonly it is used to broaden the cover of empiric therapy or to prevent the selection of resistant mutants. This latter point is well proven in the treatment of tuberculosis and HIV/AIDS and mathematical models suggest it is the best method for preventing resistance.[35] The selection of a mutant simultaneously resistant to two antibiotics is highly unlikely even at high inocula because, if the probability of a mutant arising that is resistant to each antibiotic is 1 in $10^7$ divisions, then the chance of a mutant arising that is resistant to both antibiotics would be 1 in $10^{14}$ divisions. This is a far greater number than could ever occur, even in a high inoculum infection.

Assuming the spectrum of empiric therapy is adequate, there is, in fact, little convincing evidence of improved clinical outcome when combination therapy is used.[36, 37] A few studies have identified less resistance developing where combination therapy is used, often in pseudomonal infection,[38] but recent meta analysis

of clinical trials in immunocompetent and immunocompromised patients showed no clinical benefit of combination therapy.[36, 37] The majority of the clinical trials included were, however, designed to show therapeutic equivalence between new (monotherapy) agents and standard (combination) therapy. They were not specifically designed to look for emergence of resistance, often were not analyzed on intention to treat, and cases where the isolated pathogen was not covered by the empiric therapy were excluded from the analysis.

Analysis from a recent study of pseudomonal bacteremia is intriguing. Survival was improved if both empiric and streamlined therapy were appropriate but within a subanalysis of the empiric therapy, outcome was significantly better with appropriate combination therapy over appropriate monotherapy.[39] Other recent publications on outcome of serious infection according to inhibitory quotients (multiple of the MIC) achievable in the serum cast some light on the issues, confirming the importance of the MIC of the organisms being targeted and the need to achieve serum levels several times this value. The use of inhibitory quotients to determine the adequacy of therapy is not new but has fallen out of favor due to difficulties in standardizing the test.[40, 41]

When analyzing the effects of antibiotic combinations, it is normal to categorize their interactions according to their fractional inhibitory concentration indices and to assume that synergistic combinations are best.[42] A recent analysis of antibiotic combinations against multiresistant strains of *P.aeruginosa* and *Stenotrophomonas maltophilia* in our laboratory showed no relationship between synergism and combination MICs and we have devised a new index of interaction which takes account of the MICs of the antibiotics in combination, comparing them as a ratio to the breakpoints of the respective antibiotics.[43] This breakpoint index gives one a measure of antibiotic combination activity directly related to the MICs of the antibiotics in combination and likely achievable concentration at the site of infection with standard doses. This allows direct assessment of whether the combination will achieve the critical pharmacodynamics parameters of $T > MIC$ or area under the inhibitory curve (AUIC).

In conclusion, it is likely that combination therapy will only improve outcome over appropriate monotherapy if it improves the main pharmacokinetic/pharmacodynamic (PK/PD) parameters of AUIC and $T > MIC$ or delays or prevents the emergence of resistance.

## The Role of the Microbiology Laboratory

Given the preeminence of the MIC in modern PK/PD concepts, it is obviously important, for the outcome of critical infections, that the laboratory can accurately measure the MIC of causative organisms in real time, in order to guide appropriate therapy and dosing schedules. In the absence of a pathogen or on preliminary identification, an estimate of the MICs of likely pathogens, based on data from the previous year's isolates, can be used to inform decisions on therapy. For instance, if a quinolone is being used, will low dose suffice (e.g., for a fully

susceptible *Escherichia coli*)? If possible pathogens include *A. baumannii*, which is likely to have borderline susceptible MICs, then high-dose quinolone will be more efficacious, perhaps in combination with an aminoglycoside or β-lactam.

The greatest challenge for the microbiology laboratory in the treatment of infection on the ICU is to make results available on a time scale that can influence treatment and there is reasonable hope that molecular tests will facilitate this. For bacterial infections, however, the only widely available molecular test, commonly relevant to the ICU, is PCR for the *mecA* gene of MRSA.[44] No molecular test is generally available for rapid diagnosis of invasive fungal infection, and while PCR for viral infections is making great inroads, it is outside the scope of this review.

Nevertheless, conventional culture, microscopy, and antigen-based tests generate results that are generally deliverable to the clinician in a useful time frame.[45] Sometimes the seemingly most simple problems are the most difficult to solve. Rapid delivery of specimens to the laboratory is crucial, with immediate processing either through an on-call or shift system operating in the laboratory. Then results of cell counts, Gram stains and antigen tests on CSF, urine, and other body fluids can be reported within the hour. Urine cultures (with direct susceptibility testing) can usually be read at 6 h for a clinically useful, if preliminary result. Unless received in the laboratory late the previous evening, most bronchoalveolar lavage samples (BAL), sputums, and wound cultures can be read the following morning (although anaerobic incubation takes longer) and susceptibilities predicted based on recent trends reported from the laboratory. Ninety percent of clinically significant blood cultures for bacteria will be positive within 24 h of receipt in the laboratory and a continuous monitoring system for positive results with telephoned results of Gram stain to the ICU should be standard practice.[45,46] Provisional susceptibilities and identification, including coagulase and *mecA* status where appropriate, can usually be made available in a further 6 h.

The laboratory should provide susceptibility summaries of the previous year's data for the ICU, split into community acquired, hospital acquired, ICU acquired and possibly also by body site, as susceptibilities and organisms may differ markedly depending on source.[3–5]

These results can be used to inform antibiotic guidelines for the ICU if a 24-h on-call medical microbiologist or other infection specialist is not available to advise on empiric antibiotic therapy. Rationalization of therapy at each stage of receipt of further information from the laboratory is crucial to control escalating antibiotic use. In particular, the use of broad-spectrum agents for initial empiric therapy should be changed to narrow spectrum agents at the earliest opportunity. Daily ward rounds with an infection specialist in possession of the very latest laboratory results are crucial to this process.[47,48]

The microbiologist can also help with the early detection of outbreaks, by close observation of the routine data and sometimes by the use of surveillance cultures. It is important, however, not to place too much emphasis on surveillance cultures for the choice of empiric therapy as these can have poor reliability in predicting the cause of infection and lead to overuse of antibiotics.[14, 49]

It is common now to screen all admissions to the ICU for MRSA. Isolation precautions can then be taken to prevent spread and early decolonization of MRSA-positive patients attempted.[50] Early assessment of MRSA carriage status can also inform empiric therapy should it be necessary.

## Antibiotic Prescribing Policies

If reliance is being put on a written antibiotic policy for guidance on empiric therapy, rather than 24-h advice from an infection specialist, then the policy should include advice for all common community- and hospital-acquired infections and should be informed by the previous year's susceptibility data from the laboratory. Time series analysis of these data in conjunction with hospital antibiotic use data can be used to accurately predict susceptibilities for the coming months.[51] It is usually considered appropriate to have different levels of access to different types of antibiotics in the hospital and this is probably appropriate for ICUs also, with drugs like the carbapenems, colistin, Synercid, and linezolid in a restricted access category, available only with the approval of a consultant and/or infection specialist.[52]

The need for antibiotic should be reviewed daily on every patient, always stopping at the earliest possible opportunity where the benefits of continuing are outweighed by the drawbacks—both to that patient and to the unit as a whole in terms of its microbial ecology. Ecological studies teach us that each and every gram of antibiotic adds to the selective pressure for antibiotic-resistant organisms in the hospital and this can be quantified. For example, in our hospital each extra DDD of cephalosporin prescribed per 100 patient days increases the percent MRSA in the hospital by 0.290. For quinolones and macrolides the percent increases are 0.255 and 0.165, respectively.[53]

The decision to stop therapy has to be taken on an individual basis but there is little doubt that with the advent of routine BALs, therapy for ventilator associated pneumonia (VAP) can often be stopped at 5 or 7 days where conventional wisdom was to treat for 2–3 weeks. Similarly, even the worst surgical peritonitis probably needs no more than 5 days of antibiotic therapy, providing it has been well lavaged.[54] Surgical prophylaxis should be restricted to the duration of the operation. If a second dose is needed, it should be administered during the operation. There is no benefit to prolonging prophylaxis even while drains are *in situ*.[55] Increased antibiotic use by prolonging prophylaxis increases antibiotic resistance.[56]

## Selective Digestive Decontamination and Antibiotic Cycling

There has been much debate over the past few years about these measures. In the author's opinion, the jury is still out. Selective digestive decontamination probably increases overall ICU antibiotic consumption[49] and the definitive study is still

awaited. Currently it seems to be practiced in very few ICUs.[57] There have been fewer studies published on antibiotic cycling and none looking at it over the long term.[6, 12, 58] Benefits are dubious, possibly as there are not enough different classes of antibiotic to cycle and many of them share common resistance mechanisms such as enzyme degradation, efflux, and impermeability. Mathematical models do not suggest it is an efficient way of preventing resistance.[35]

## Empiric Treatment Choices for Multiresistant Organisms

These are summarized in Table 13.1. For understandable reasons there are few randomized clinical studies. Recent comparative studies of linezolid versus vancomycin or teicoplanin in VAP and skin and soft tissue infections (SSTI)[59, 60] show superiority of linezolid in MRSA infections on subanalysis but no studies

TABLE 13.1. Suggested empiric treatments while awaiting confirmation of susceptibility for life-threatening infection due to common ICU infections[a, b]

| Infecting organisms[c] | First choice | Second choice |
|---|---|---|
| MRSA | Vancomycin[d] ± rifampicin[e] | Linezolid ± rifampicin[f] |
| VRE | Linezolid ± rifampicin or amoxicillin[g] | Quinupristin/dalfopristin[h] ± rifampicin |
| GISA/VRSA | Linezolid ± rifampicin | Quinupristin/dalfopristin ± ampicillin/sulbactam |
| ESBL producer | Carbapenem | Temocillin or tigecycline[h] ± aminoglycoside |
| Carbapenemase producer | Aminoglycoside[g] ± quinolone[i] | Colistin + [g] |
| Inducible Enterobacteriaceae | Quinolone[i] ± aminoglycoside[g] | Carbapenem |
| *P.aeruginosa* | Piperacillin/tazobactam ± aminoglycoside[g] | Colistin ± aminoglycoside[g] |
| *Acinetobacter* spp. | Carbapenem ± aminoglycoside[g] | Ampicillin/sulbactam ± tetracycline |
| *S. maltophilia* | Ceftazidime + co-trimoxazole | Ticarcillin ± aminoglycoside |

[a] Note: this table should always be used in conjunction with previous susceptibility data from your local laboratory which will highlight the presence of local epidemic strains and resistance problems.

[b] Always streamline therapy on receipt of susceptibilities in order to keep the use of broad-spectrum agents to a minimum.

[c] MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus* spp.; GISA/VRSA, glycopeptide intermediate *Staphylococcus aureus*/vancomycin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum β-lactamase producer.

[d] Keep trough at 20 mg/liter.

[e] If bacteremic, delay rifampicin for 2 days.

[f] To prevent selection of resistance to linezolid.

[g] Depends on local susceptibilities.

[h] Not *E. faecalis*.

[i] Ciprofloxacin is generally the most active against the Enterobacteriaceae but should be used in high dose—IV 400 mg TID or PO 1 g BD.

have compared linezolid against a glycopeptide in combination with another agent. Such combination therapy is now commonplace with the realization that the glycopeptides, while long thought to be the last option for MRSA, are only slowly bactericidal, have poor tissue penetration, are much less active than flucloxacillin against antibiotic susceptible *S. aureus* (MSSA), and have a 50% failure rate when used as monotherapy in MRSA VAP.[29, 61, 62] In MRSA bacteremia it may be wise to delay addition of rifampicin to vancomycin therapy for 48 h to allow time for adequate tissue penetration of the glycopeptide and in case the rifampicin delays clearance of the bacteremia by inhibiting the already limited bactericidal activity of the glycopeptide (W. Craig personal communication).

In all cases, local susceptibility patterns should be consulted if using Table 13.1 as a guide for empiric therapy as the susceptibility of local isolates or epidemic clones can vary markedly. At the moment, quinupristin/dalfopristin and linezolid resistance are rarely reported in MRSA or vancomycin-resistant *E. faecium*.[63, 64] High-level vancomycin resistance in MRSA is also uncommon[65] although glycopeptide intermediate *S. aureus* (GISA)[66] and ESBL producers are probably underreported due to laboratory ascertainment problems.[67] ESBLs probably remain uncommon in non-Enterobacteriaceae. Carbapenemases, while uncommon in most countries, are definitely on the increase through plasmid-mediated spread and are already a major problem in Enterobacteriaceae and *A. baumannii* in some regions.[10–13] *S. maltophilia* is naturally resistant to most antibiotics although aminoglycoside resistance tends to be low level, often allowing benefits from combination therapy.[43] Quinolone resistance is highly variable but broadly increasing in all Enterobacteriaceae and plasmid-mediated resistance is a major new concern.[68]

In summary, optimization of antibiotic therapy in the ICU is difficult but important and is not going to get any easier with increasing problems of multiresistance. Close liaison with the laboratory is crucial and every effort must be made to receive and act on laboratory results as quickly as possible to optimize therapy according to modern PK/PD principles and also to streamline therapy as much as possible to reduce ecological pressures for the selection of further multiresistance.

## *References*

1. Martin, G.S., Mannino, D.M., Eaton, S., & Moss, M. 2003. The epidemiology of sepsis in the United States from 1979 through 2000. *The New England Journal of Medicine* 348:1546–54.
2. Vincent, J.-L. 2003. Nosocomial infections in adult intensive-care units. *The Lancet* 361:2068–77.
3. McGowan, J.E., & Tenover, F.C. 2004. Confronting bacterial resistance in healthcare settings: A crucial role for microbiologists. *Nature* 2:251–8.
4. Fridkin, S.K., Hill, H.A., Volkova, N.V., Edwards, J.R., Lawton, R.M., Gaynes, R.P., McGowan, J.E., et al. 2002. Temporal changes in prevalence of antimicrobial resistance in 23 U.S. hospitals. *Emerging Infectious Diseases* 8:697–701.
5. Fridkin, S.K. 2001. Increasing prevalence of antimicrobial resistance in intensive care units. *Critical Care Medicine* 29(Suppl):N64–N68.

6. Gould, I.M. 2001. Antibiotic rotation to control resistance, in Gaffey, H.F. (ed.). *Critical Care Focus*. pp 41–7.
7. Gould, I.M. 2000. A review of the role of antibiotic policies in the control of antibiotic resistance. *Journal of Antimicrobial Chemotherapy* 43:459–65.
8. Paramythiotou, E., Lucet, J., Timsit, J., Vanjak, D., Paugam-Burtz, C., Trouillet, J., Belloc, S., et al. 2004. Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: Role of antibiotics with antipseudomonas activity. *Clinical Infectious Diseases* 38:670–7.
9. El Shafie, S.S., Alishaq, M., & Garcia, M.L. 2004. Investigation of an outbreak of multi-drug resistant *Acinetobacter baumannii* in trauma intensive care unit. *Journal of Hospital Infection* 56:101–5.
10. Corbella, X., Montero, A., Pujol, M., Domínguez, M.A., Ayats, J., Argerich, M.J., Garrigosa, F., et al. 2000. Emergence of rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii. Journal of Clinical Microbiology* 38:4086–95.
11. Johnson, A.P., Henwood, C., Mushtaq, S., Warner, J.M., Livermore, D.M., The ICU Study Group. 2003. Susceptibility of Gram-positive bacteria from ICU patients in UK hospitals to antimicrobial agents. *Journal of Hospital Infection* 54:179–87.
12. Puzniak, L.A., Mayfield, J., Leet, T., Kollef, M., & Mundy, L.M. 2001. Acquisition of vancomycin-resistant enterococci during scheduled antimicrobial rotation in an intensive care unit. *Clinical Infectious Diseases* 33:151–7.
13. Rodriguez-Villalobos, H., Struelens, M.J., Jones, & R.N. 2003. Resistance in pathogens from patients admitted to intensive care unit (ICU): A report from the SENTRY surveillance program, Europe 2000–2002. Abstract C2-1971. *43rd ICAAC*, American Society for Microbiology, p. 148.
14. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 to June 2002, issued August 2002. 2002. *American Journal of Infection Control* 30:458–75.
15. Fridkin, S.K., Lawton, R., Edwards, J.R., Tenover, F.C., McGowan, J.E., Gaynes, R.P., the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project and the National Nosocomial Infections Surveillance (NNIS) System Hospitals. 2002. Monitoring antimicrobial use and resistance: Comparison with a national benchmark on reducing vancomycin-resistant enterococci. *Emerging Infectious Diseases* 8:702–7.
16. Lagatolla, C., Tonin, E.A., Monti-Bragadin, C., Dolzani, L., Gombac, F., Bearzi, C., Edalucci, E., et al. 2004. Endemic carbapenem-resistant Pseudomonas aeruginosa with acquired metallo-β-lactamase determinants in European hospital. Emerging Infectious Diseases 10:535–8.
17. Lee, S., Kim, J., Choi, S., Kim, T., Chung, J., Woo, J., Ryu, J., et al. 2004. Risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii*: A case–control study. *Antimicrobial Agents and Chemotherapy* 48:224–8.
18. Shannon, K.P., & French, G.L. 2004. Increasing resistance to antimicrobial agents of Gram-negative organisms isolated at a London teaching hospital, 1995–2000. *Journal of Antimicrobial Chemotherapy* 53:818–25.
19. Garnacho-Montero, J., Garcia-Garmendia, J.L., Barrero-Almodovar, A., Jiminez-Jiminez, F.J., Perez-Parades, C., & Ortiz-Leyba, C. 2003. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Critical Care Medicine* 31:2742–51.
20. Kang, C., Kim, S., Kim, H., Park, S., Choe, Y., Oh, M., Kim, E., et al. 2003. *Pseudomonas aeruginosa* bacteremia: Risk factors for mortality and influence of delayed receipt

of effective antimicrobial therapy on clinical outcome. *Clinical Infectious Diseases* 37:745.
21. Gould, I.M., & MacKenzie, F.M. 1997. The response of Enterobacteriaceae to β-lactam antibiotics—"Round forms, filaments and the root of all evil." Journal of Antimicrobial Chemotherapy 40:495–9.
22. Gould, I.M., & MacKenzie, F.M. 2002. Antibiotic exposure as a risk factor for emergence of resistance: The influence of concentration. *Journal of Applied Microbiology* 92(Suppl 1):78S–84S.
23. Drenkare, E., & Ausubel, F.M. 2002. *Pseudomonas* biofilm formation and antibiotic resistance are linked to phenotype variation. *Nature* 416:740–3.
24. Blázquez, J. 2003. Hypermutation as a factor contributing to the acquisition of antimicrobial resistance. *Clinical Infectious Diseases* 37:1201–9.
25. Pankey, G.A., & Sabath, L.D. 2004. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clinical Infectious Diseases* 38:864–70.
26. Celfand, J.A., Elin, R.J., Berry, F.W., et al. 1976. Endotoxemia associated with the Jarisch-Herxheimer reaction. *New England Journal of Medicine* 295:211.
27. McKinnon, P.S., & Davis, S.L. 2004. Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. *European Journal of Clinical Microbiology & Infectious Diseases* 23:271–88.
28. Drusano, G.L. 2004. Antimicrobial pharmacodynamics: Critical interactions of "bug and drug." *Nature* 2:289–300.
29. Schentag, J.J. 2001. Antimicrobial management strategies for Gram-positive bacterial resistance in the intensive care unit. *Critical Care Medicine* 29:100–7.
30. McKenzie, F.M., Gould, I.M., Chapman, D.G., & Jason, D. 1994. The post antibiotic effect of meropenem on members of the family Enterobacteriaceae determined by five methods. *Antimicrobial Agents & Chemotherapy* 38:2583–9.
31. Benko, A.S., Cappelletty, D.M., Kruse, J.A., & Rybak, M.J. 1996. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected Gram-negative infections. *Antimicrobial Agents & Chemotherapy* 40:691–5.
32. Buabeng, K.O., MacKenzie, A.R., Laing, R.B.S., Cook, I., Jappy, B. & Gould, I.M. 1999. Assessment of the efficacy, safety and quality of gentamicin use in Aberdeen Royal Infirmary. *Journal of Antimicrobial Chemotherapy* 45:843–5.
33. Smith, S.V., & Gould, I.M. 2004. Optimization of antibiotic dosing schedules in the light of increasing antibiotic resistance. *Expert Review of Anti-infective Therapies* 2:89–96.
34. Gould, I.M. 2001. Measurement of antibiotic efficacy—Beyond the MIC. *Journal of Chemotherapy* 13:12–6.
35. Lipstitch, M., Bergstrom, C.T., & Levin, B.R. 2000. The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions. *PNAS* 97:1938–43.
36. Paul, M., Benuri-Silbiger, I., Soares-Weiser, K., & Leibovici, L. 2004. β lactam monotherapy versus lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: Systematic review and meta-analysis of randomised trials. British Medical Journal 328:668–72.
37. Paul, M., Soares-Weiser, K., & Leibovici, L. 2003. β lactam monotherapy versus lactam-aminoglycoside combination therapy for fever for neutropenia: Systematic review and meta-analysis. British Medical Journal 326:1111–5.
38. Gould, I.M. 1994. Risk factors for acquisition of multiply-resistant Gram negative bacteria. *European Journal Clinical Microbiology and Infectious Diseases* 13:30–8.

39. Chamot, E., El Amari, E.B., Rohner, P., & Van Delden, C. 2003 Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteraemia. *Antimicrobial Agents and Chemotherapy* 47:2756–64.
40. Zelenitsky, S.A., Harding, G.K.M., Sun, S., Ubhi, K., & Ariano, R.E. 2003. Treatment and outcome of *Pseudomonas aeruginosa* bacteraemia: An antibiotic pharmacodynamic analysis. *Journal of Antimicrobial Chemotherapy* 52:668–74.
41. Spanu, T., Santangelo, R., Andreotti, F., Lo Cascio, G., Velardi, G., & Fadda, G. 2004. Antibiotic therapy for severe bacterial infections: Correlation between the inhibitory quotient and outcome. *International Journal of Antimicrobial Agents* 23:120–8.
42. Mackay, M.L., Milne, K., & Gould, I.M. 2000. Comparison of methods for assessing synergic antibiotic interactions. *International Journal of Antimicrobial Agents* 15:125–9.
43. Gould, I.M., Milne, K., & MacKenzie, F.M. 2004. The breakpoint index—a new pharmacodynamic parameter for assessing antibiotic combinations. *14th* ECCMID, Prague, Abstract P1796.
44. Bignardi, G.E., Woodford, N., Chapman, A., Johnson, A.P., & Speller, D.C. 1996. Detection of the mec-A gene and phenotypic detection of resistance in *Staphylococcus aureus* isolates with borderline or low-level methicillin resistance. *Journal of Antimicrobial Chemotherapy* 37:53–63.
45. Mackenzie, A.R., Robertson, L., Jappy, B., Laing, R.B.S., & Gould, I.M. 2003. Audit of an antibiotic policy and microbiological investigations for treating bacteraemia in a large teaching hospital. *International Journal of Antimicrobial Agents* 22:618–21.
46. Cunney, R.J., & Smyth, E.G. 2000. The impact of laboratory reporting practice on antibiotic utilisation. *International Journal of Antimicrobial Agents* 14:13–9.
47. Scottish Infections Standards and Strategies (SISS) Group. 2003. Good practice guidance for antibiotic prescribing in hospital. *Journal of the Royal College of Physicians of Edinburgh* 33:281–4.
48. Gould, I.M. 2004 Antibiotic use—Ecological issues and required actions, in Gould, I.M., & van Der Meer, J. (ed *Antibiotic Theory & Practice*. Kluwer, Amsterdam, pp 702–15.
49. Monnet, D.L., Suetens, C., Jepsen, O.B., Burman, L.G., Carsauw, H., Gastmeier, P., Jurkuvenas, V., Sainz, A., the European Strategy for Antibiotic Prophylaxis (ESAP) Project Team. 2000. Overall antimicrobial use and control strategies in intensive care units from 6 European countries (abstract P-S2–03). *4th Decennial International Conference on Nosocomial and Healthcare-Associated Infections*, Atlanta, Georgia, USA. *Infection Control and Hospital Epidemiology* 21:88.
50. Chaix, C., Durand-Zaleski, I., Alberti, C., & Brun-Buisson, C. 1999. Control of endemic methicillin-resistant *Staphylococcus aureus. Journal of the American Medical Association* 282:1745–51.
51. Lopez-Lozano, J.M., Monnet, D.L., Yague, A., Burgos, A., Gonzalo, N., Campillos, P., & Saez, M. 2000. Modelling and forecasting antimicrobial resistance and its dynamic relationship to antimicrobial use: A time series analysis. *International Journal of Antimicrobial Agents* 14:21–31.
52. Gould, I.M., Hampson, J., Taylor, E., & Wood, M. 1994. Hospital antibiotic control measures in the UK—Results of a BSAC Working Party Survey. *Journal of Antimicrobial Chemotherapy* 34:21–42.
53. Monnet, D.L., MacKenzie, F.M., López-Lozano, J.M., Beyaert, A., Carmacho, M., Wilson, R., Stuart, D., et al The role of antimicrobial use in the Aberdeen MRSA outbreak 1996–2000. *Emerging Infectious Diseases* 2004; 10: 1432–41

54. Gleisner, A.L.M., Argenta, R., Pimental, M., Simon, T.K., Jungblut, C.F., Petteffi, L., de Souza, R.M., et al 2004. Infective complications according to duration of antibiotic treatment in acute abdomen. *International Journal of Infectious Diseases* 8:155–62.
55. Scottish Intercollegiate Guidelines Network. 2000. *Antibiotic Prophylaxis in Surgery. A National Clinical Guideline*. Publication No. 45. London, Royal College of Physicians.
56. Harbarth, S., Samore, M.H., Lichtenberg, D., & Carmeli, Y. 2000. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* 101:2916–21.
57. Aarts, M., & Marshall, J.C. 2002. In defense of evidence. The continuing saga of selective decontamination of the digestive tract. *American Journal of Respiratory and Critical Care Medicine* 166:1014–5.
58. Kollef, M.H. 2001. Is there a role for antibiotic cycling in the intensive care unit? *Critical Care Medicine* 29:135–42.
59. Wunderink, R.G., Rello, J., Cammarata, S.K., Croos-Dabrera, R.V., & Kollef, M.H. 2003. Linezolid vs vancomycin. *Chest* 124:1789–97.
60. Wilcox, M., Nathwani, D., & Dryden, M. 2004. Linezolid compared with teicoplanin for the treatment of suspected or proven Gram-positive infections. *Journal of Antimicrobial Chemotherapy* 53:335–44.
61. Ioanas, M., & Lode, H. 2004. Linezolid in VAP by MRSA: A better choice? *Intensive Care Medicine* 30:343–6.
62. Kollef, M.H., Rello, J., Cammarata, S.K., Croos-Dabrera, R.V., & Wunderink, R.G. 2004. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: Retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Medicine* 30:388–94.
63. Moellering, R.C., Linden, P.K., Reinhardt, J., Blumberg, E.A., Bompart, F., & Talbot, G.H. 1999. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium. Journal of Antimicrobial Chemotherapy* 44:251–61.
64. Baysallar, M., Kilic, A., Aydogan, H., Cilli, F., & Doganci, L. 2004. Linezolid and quinupristin/dalfopristin resistance in vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* prior to clinical use in Turkey. *International Journal of Antimicrobial Agents* 23:510–20.
65. Tenover, F.C., Weigel, L.M., Appelbaum, P.C., McDougal, L.K., Chaitram, J., McAllister, S., Clark, N., et al 2004. Vancomycin-resistant *Staphylococcus aureus* isolate from a patient in Pennsylvania. *Antimicrobial Agents & Chemotherapy* 48:275–80.
66. MacKenzie, F.M., Greig, P., Morrison, D., Edwards, G., & Gould, I.M. 2002. Identification and characterization of teicoplanin-intermediate *Staphylococcus aureus* blood culture isolates in NE Scotland. *Journal of Antimicrobial Chemotherapy* 50:689–97.
67. MacKenzie, F.M., Miller, C., & Gould, I.M. 2002. Comparison of screening methods for TEM- and SHV-derived extended-spectrum β-lactamase detection. Clinical Microbiology & Infection 11:715–24.
68. Cheung, T.K.M., Chu, Y.W., Chu, M.A., Ma Ha, C., Yung, R.W., & Kam, K.M. 2005. Plasmid-mediated resistance to ciprofloxacin and cefotaxime in clinical isolates of *Salmonella enterica* serotype enteritidis in Hong Kong. *Journal of Antimicrobial Chemotherapy* 56:586–9.

# Chapter 14
# Risk Assessment for Methicillin-Resistant *Staphylococcus aureus*

Evelind Tacconelli

## Foreword

Nosocomial infections pose a significant threat to patients worldwide. A recent paper reported excess mortality of 4% for infections due to medical care and 23% mortality for postoperative septicemia (Zhan and Miller 2003). Antibiotic resistant bacteria cause the majority of these nosocomial infection-related deaths. European surveillance has documented that methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multidrug-resistant gram-negative bacteria are rapidly increasing (Biedenbach et al. 2004). In the United States the National Nosocomial Infections Surveillance (NNIS) data demonstrated in 2002 that the frequencies of MRSA, methicillin-resistant coagulase-negative (MR-CoNS), and VRE from intensive care units (ICUs) were 57, 89, and 27%, respectively (CDC, NNIS System 2003).

The endemic state of nosocomial infections resistant to antibiotics is caused by a constant influx of microorganisms into the health care setting (as for MRSA and VRE) from newly admitted patients who are colonized or infected with antibiotic-resistant bacteria, followed by cross-transmission between hospitalized patients with *de novo* acquisition and efflux of antibiotic-resistant bacteria from the hospitals into the community after patients' discharge.

To develop effective prevention strategies it is necessary to understand the various components required to achieve this endemic state. Up to now the majority of prevention strategies have focused on the middle component as with hospital guidelines for antibiotic therapy and prevention of cross-transmission between hospitalized patients and hospital staff and patients. However, the influx of antibiotic-resistant bacteria into the health care setting may be an even more important factor in establishing endemicity. In a cohort of patients with MRSA and VRE bacteremia stratified by day of hospitalization, an unexpected high number of cases were diagnosed within 48 hours of hospitalization (Huang et al. 2002). A mathematical model describing the transmission dynamics of VRE demonstrated that eradication could be achieved by prevention of this influx (D'Agata et al. 2002). This model demonstrated that, although 100% compliance with hand washing or a 1:1 nurse-to-patient ratio would substantially decrease

the overall prevalence of VRE in the unit, preventing the influx of VRE into the unit was the only intervention that achieved a complete eradication of VRE from this patient population over time.

Therefore, it seems of paramount importance to define epidemiological characteristics of patients at higher risk for being infected or colonized with MRSA, the most frequent isolated antibiotic-resistant bacteria, both at hospital admission and during hospitalization. This would allow physicians to carry out specific screening procedures and control measures and to start the most appropriate empirical therapy to reduce the spread of MRSA infections and the related mortality.

## Risk Assessment for MRSA at Hospital Admission

Although previously considered a purely nosocomial pathogen, recovered from hospitalized patients only, MRSA is now being recovered with increasing frequency at hospital admission (Eveillard et al. 2002, Huang et al. 2002, Tacconelli et al. 2004a). In an outpatient military clinic, MRSA colonization was present in 2% of screened patients with a tendency to be more frequent in men, those who were older, or with previous hospitalizations (Kenner et al. 2003).

These "community-acquired" MRSA strains arise from two different patient populations: those with "true" community-acquired MRSA strains which have emerged *de novo* from community-based *S. aureus* strains in specific populations as in children, inmates, and military personnel, and "health care-associated" strains which have been acquired in the hospital during a recent exposure to a health care setting or surgical procedures (Charlebois et al. 2002, Weber 2005). A meta-analysis of MRSA infections identified within 24–72 hours of hospitalization, documented a prevalence of community-acquired MRSA infections, defined as patients without any known risk factors for harboring MRSA, of $\leq 0.24\%$ (Salgado et al. 2003). These "truly" community-acquired MRSA strains are frequently associated with skin infections, particularly in children, and tend to be susceptible to more antibiotics and are genetically distinct from health care-associated strains (Fridkin et al. 2005).

The population with a recent exposure to health care center is twice as likely to harbor MRSA compared to persons with no exposure (Rubinovitch and Pittet 2001). This changing epidemiology has likely led to an increase in the number of patients with MRSA infections or colonization diagnosed at hospital admission.

MRSA colonization might also occur frequently among household contacts of patients with nosocomial-acquired MRSA. In a retrospective cohort study MRSA was isolated among households and community contacts of MRSA-colonized or -infected patients with a prevalence of 14.5% (Calfee et al. 2003). In geriatric departments, carriage among health care workers, assisting patients in contact precaution for MRSA, ranged from 0% to 3.3%. Carriage, usually transient, was observed only among nurses and nursing assistants (Scarnato et al. 2003).

Comparing patients with MRSA bacteremia to those with methicillin-susceptible *S. aureus* (MSSA) bacteremia diagnosed on admission to a 1000-bed public hospital in the United States, variables independently associated with the development of MRSA bacteremia were hospitalization in the previous 6 months, antimicrobial therapy in the previous 3 months, central venous catheter (CVC), and nursing home residency. In particular, the use of antimicrobial therapy increased the risk of MRSA bacteremia versus MSSA bacteremia by six fold (Rezende et al. 2002).

Therefore, the majority of patients with MRSA diagnosed within 48 hours of hospital admission are to be considered health care associated infections or colonizations.

According to Friedman and co-workers (2002), the health care-associated infected patient was defined as a subject who fulfilled any of the following criteria: intravenous therapy within 30 days; specialized nursing at home; attendance to a hospital or outpatient clinic for dialysis; previous hospitalization for at least 2 days within 90 days; residency in a nursing home or long term care facility. This separate category of infection, differentiated from the community- and nosocomial-acquired infections, was justified since these infections were similar to nosocomial infections in terms of frequency of various comorbidity, source of infection, pathogens, susceptibility patterns, and mortality rate. A significant impact for physicians of this new categorization of infections would be on the choice of empirical therapy for infections diagnosed at hospital admission and for infection-control policies. In a case–control study including 108 patients with true CoNS bacteremia diagnosed within 48 hours of hospital admission the probability of infection caused by a methicillin-resistant strain, compared to a methicillin-susceptible strain was 62% in patients admitted from the community and 84% in patients admitted from health care facilities (Tacconelli et al. 2003b).

In a cohort study of 127 patients with health care-associated MRSA bacteremia diagnosed at hospital admission, using logistic regression analysis, independent risk factors included a history of MRSA colonization or infection within 90 days, presence of a CVC, and skin ulcers or cellulitis. Excluding from the statistical model prior history of MRSA, since knowledge of this information may not always be available at the time of hospital admission, the presence of a CVC, prior hospitalization within 90 days, diabetes mellitus, and quinolone therapy within 30 days were also associated with MRSA bacteremia at hospitalization (Tacconelli et al. 2004b; Table 14.1). The differences between the two analyses suggest that a prior history of MRSA colonization or infection may be an indicator of the other risk factors identified in the second analysis, all of which have been previously recognized to increase the likelihood of harboring MRSA (Graffunder and Venezia 2002).

Risk assessment of MRSA on admission to the ICU deserves special attention because of the severity of underlying diseases in such a population. Whether MRSA screening at ICU admission is worthwhile remains a matter of debate. British and U.S. guidelines recommend that patients be screened routinely before ICU admission in a hospital where MRSA is endemic (Working Party Report 1998; Mangram et al. 1999). Prevalence of MRSA colonization reported from

TABLE 14.1. Two logistic regression analyses of risk factors associated with health care-associated MRSA bacteremia at hospital admission, including (first model) and excluding (second model) a history of previous MRSA infection or colonization[a]

| Variables | OR | 95% CI | p value |
|---|---|---|---|
| First model | | | |
| Previous MRSA infection or colonization | 17 | 5–58.3 | < 0.001 |
| Cellulitis at hospital admission | 4.3 | 1.5–11.9 | 0.006 |
| Presence of a central venous catheter | 3.3 | 1.7–6.4 | < 0.001 |
| Skin ulcers at hospital admission | 3.1 | 1.4–7.1 | 0.007 |
| Second model | | | |
| Presence of a central venous catheter | 3.2 | 1.8–6 | < 0.001 |
| Hospitalization in the previous 6 months | 2 | 1.1–3.6 | 0.02 |
| Quinolone therapy in the previous 30 days | 2 | 1.1–3.7 | 0.02 |
| Diabetes mellitus | 1.8 | 1.1–3.2 | 0.03 |

[a] Adapted from Tacconelli et al. (2004b).

different studies in ICUs varies from 3.7% to 20% according to local epidemiological situation. In a prospective study including 484 patients consecutively admitted at a surgical ICU in the United States, 3.9% of patients had nasal colonization with MRSA. Positive patients developed more frequent MRSA infections compared to negative patients and were more likely to have had exposure to antibiotic therapy and to the spinal cord injury center (Mest et al. 1994). In an endemic setting in France, the prevalence of MRSA carriage at ICU admission was 6.9%. Factors associated with MRSA carriage were age older than 60 years, transfer from other departments or hospitals, prolonged length of hospitalization in other wards, previous hospitalization in surgery, and presence of open skin lesions. With a cost–benefit analysis the authors demonstrated that, in their epidemiological setting, universal screening and isolation were beneficial. The cost of screening all patients regardless of the presence of risk factors was less expensive than the overall treatment of MRSA infections prevented by the screening. The second best strategy was limiting the screening to transferred patients and to patients with at least one risk factor. On the contrary, limiting the screening to patients with more than one risk factor was more costly than the MRSA treatment of prevented infections (Lucet et al. 2003). Papia et al. (1999) showed that if an early identification of MRSA in colonized patients at hospital admission reduced nosocomial transmission of the organism to as few as six new patients per year, the screening program would be cost-effective.

In a recent paper Eveillard and co-workers (2005) evaluated the impact of different components of a screening program of MRSA carriers at hospital admission on the value of two risk-adjusted rates: the proportion of imported MRSA as an indicator of the MRSA colonization pressure (ICP) and the incidence of nosocomial-acquired MRSA. Screening patients with risk factors resulted in a 51% increase of the calculated proportion of imported strains and a 58% decrease of the ICP.

Multiple bacterial colonization may also be frequent at ICU admission (Furuno et al. 2005). Many MRSA-positive patients could be co-colonized with MRSA and VRE. In the United States co-colonization with VRE and MRSA was described in 3% of hospitalization to an ICU at a tertiary-care hospital. Risk factors in these patients were advanced age, male sex, and antimicrobial therapy within 1 year (Furuno et al. 2005).

To help physicians in defining high-risk patients for MRSA or VRE carriage on hospital admission, prediction rules were elaborated. Prior hospitalizations within 1 year had a sensitivity of 56.8% and a specificity of 88.4% in identifying MRSA or VRE carriers at hospital admission in non-ICUs (Furuno et al. 2004).

A specific score for VRE was elaborated and then validated in two university hospitals in Boston (USA) using six independent risk factors associated with VRE recovery within 48 hours of hospital admission: previous isolation of MRSA (4 points), chronic hemodialysis (3 points), admission from a long term chronic facility (3 points), antibiotic exposure (3 points), prior hospitalization (3 points), and age $>$ 60 years (2 points). Using a point score of $\geq$ 10, the sensitivity, specificity, positive and negative predictive values of this prediction rule were 44, 98, 81, and 90%, respectively (Tacconelli et al. 2004a, Figure 14.1). In an elderly population, two prospective case–control studies derived a risk score that estimated the likelihood of unknown MRSA carriers at hospital admission (Sax et al. 2005). In this population risk factors were: recent antibiotic therapy, in-hospital transfers, and hospitalization in the last 2 years.

The knowledge of MRSA risk assessment in patients on hospital admission using validated prediction rules can help in identifying a subgroup of patients who are at high risk of being MRSA carriers or with MRSA infections among all patients admitted from out-of-hospital settings or who have recently had exposure to a health care intervention. The knowledge of local epidemiological characteristics of

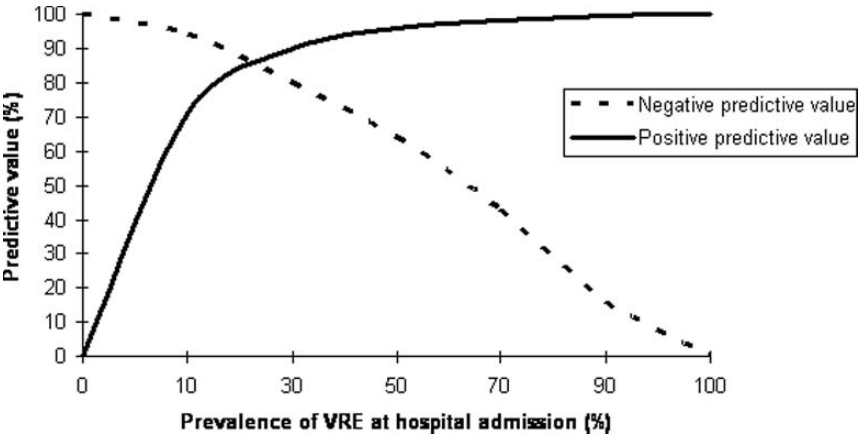



FIGURE 14.1. Negative and positive predictive values of the risk score identifying VRE-positive patients at hospital admission according to increasing prevalence of patients with VRE. Adapted from Tacconelli et al. (2004).

population admitted to the hospital is also fundamental to define risk factors in a specific epidemiological situation. Empiric use of vancomycin in patients with high suspicion of MRSA infections may be warranted in the presence of symptoms and signs consistent with bacteremia (Tacconelli et al. 2004b). Identification of carriers may also warrant prompt institution of infection control interventions to limit cross-transmission between colonized patients, hospital personnel, and non-colonized patients.

## Risk Assessment for MRSA During Hospitalization

Epidemiology of nosocomial acquisition of MRSA is well described in numerous reports (Grundmann et al. 2002, Graffunder and Venezia 2002, Campbell et al. 2003). Risk factors include: underlying disease, prior hospitalization, prior antimicrobial use, prior surgery, length of hospitalization, central venous catheterization and endotracheal intubation, enteral feeding, admission to ICU, nursing staff work load, and compliance with hand disinfection procedures (Grundmann et al. 2002, Graffunder and Venezia 2002, Campbell et al. 2003). Specific analysis of antibiotic exposure showed that quinolones (i.e., levofloxacin and ciprofloxacin) and macrolides were associated with MRSA but not with MSSA isolation (Graffunder and Venezia 2002, Weber et al. 2003).

A 1-year study carried out at an ICU in a U.K. university hospital showed, using a multivariate model, that urgent admission, value of APACHE II score at 24 hours, bronchoscopy, and days of staff deficit were all independent risk factors for nosocomial MRSA acquisition. Fitting a simple stochastic model they also documented that exposure to staff shortage was the only factor significantly associated with cross-transmission. It was predicted that a 12% improvement in adherence to hand hygiene might have compensated for staff shortage and prevented transmission during periods of overcrowding, shared care, and high work load but that this would be hard to achieve (Grundmann et al. 2002). The risk to patients in terms of nosocomial transmission of MRSA also seems to be significantly influenced by the proportion of patients with colonization at ICU admission regardless of the size of the ICU (Ho 2003).

The importance of hospital infection control policies was demonstrated also in non-ICUs. Schelenz and co-workers (2005) with an enhanced control program based on U.K. national guidelines observed, in a department of cardiothoracic surgery, a significant reduction in the proportion of patients acquiring MRSA on the ward and in the rate of bacteremia due to MRSA.

Interestingly, the distribution of risk factors for nosocomial acquisition of MRSA seems also to be related to the type of disease caused by the microorganism. Invasive disease was more frequently observed in male patients with underlying conditions in contrast to patients with skin infections (Buck et al. 2005).

Risk assessment for MRSA might also be different in specific populations, such as patients with HIV infection. In retrospective case–control studies, prior hospitalization, exposure to broad spectrum antibiotics, presence of a CVC,

dermatological disease, APACHE III score, and HIV viremia were independent risk factors for the development of MRSA infection or colonization (Onorato et al. 1999, Tumbarello et al. 2002).

Among the strategies aimed at reducing MRSA nosocomial infections, the identification of MRSA-positive patients at hospital discharge might have a pivotal role. Many studies demonstrated a strong association between hospital-acquired colonization and development of subsequent infections (Garrouste-Orgeas et al. 2001, Huang and Platt 2003). Differences in the assessment of the risk of MRSA-associated sequelae might be related to the length of follow up in different studies. In an 18-month follow-up, 29% of patients with MRSA colonization at hospital discharge presented with infections. The majority of infections developed in a site unrelated to the initial site from which MRSA was isolated. The risk of subsequent MRSA infection exceeds 30% in colonized ICU patients (Garrouste-Orgeas et al. 2001).

This high risk of subsequent infection increases the need to eradicate MRSA carriage particularly in patients with severe underlying diseases, such as those in ICU or surgical wards or hemodialysis patients. Of even more concern are the recent reports of *S. aureus* isolates resistant to vancomycin and linezolid, recovered from chronic hemodialysis patients (Tsiodras et al. 2001, CDC 2002).

Mupirocin is a topical antibacterial ointment, which has demonstrated benefit in eradicating colonization with *S. aureus* (Chow and Yu 1989, Wilcox et al. 2003). Perl and co-workers (2002) demonstrated in a randomized, double-blind, placebo controlled trial that prophylaxis with intranasal mupirocin was associated with a reduction of the rate of all nosocomial infections caused by *S. aureus* in patients who where *S. aureus* Carries.

The efficacy of mupirocin in preventing *S. aureus* infections, however, is controversial especially in patients after gastrointestinal surgery and in transplant patients (Paterson et al. 2003, Suzuki et al. 2003). Discordant results among published studies and varying estimates of the risk reduction may be due to differences in study design and patient population, mupirocin regimen, or type and definition of infection. There are also concerns regarding the emergence of mupirocin resistance among *S. aureus* isolates (Miller et al. 1996).

A systematic review of the English language literature was performed to determine the overall benefit of mupirocin therapy in reducing the rate of *S. aureus* infection among high-risk patients requiring chronic hemodialysis (HD) or peritoneal dialysis (PD) (Tacconelli et al. 2003a). A total of 10 clinical studies were evaluated with 1212 patients in the treatment group and 1233 in the control group. Overall, mupirocin therapy reduced the risk of developing an *S. aureus* infection by 68% among all dialysis patients (Figure 14.2). In a subgroup analysis of different dialysis modalities, the risk reduction was 80% for HD and 63% for PD patients, respectively. Analysis of different types of *S. aureus* infections, including exit-site infection, peritonitis, and bacteremia, demonstrated significant reductions among patients receiving mupirocin therapy.

Laupland and Conly (2003) appraised the efficacy of mupirocin in eradicating *S. aureus* nasal carriage and preventing infections in different populations: health care workers, HIV-infected individuals, and hemodialysis patients. In their analysis,

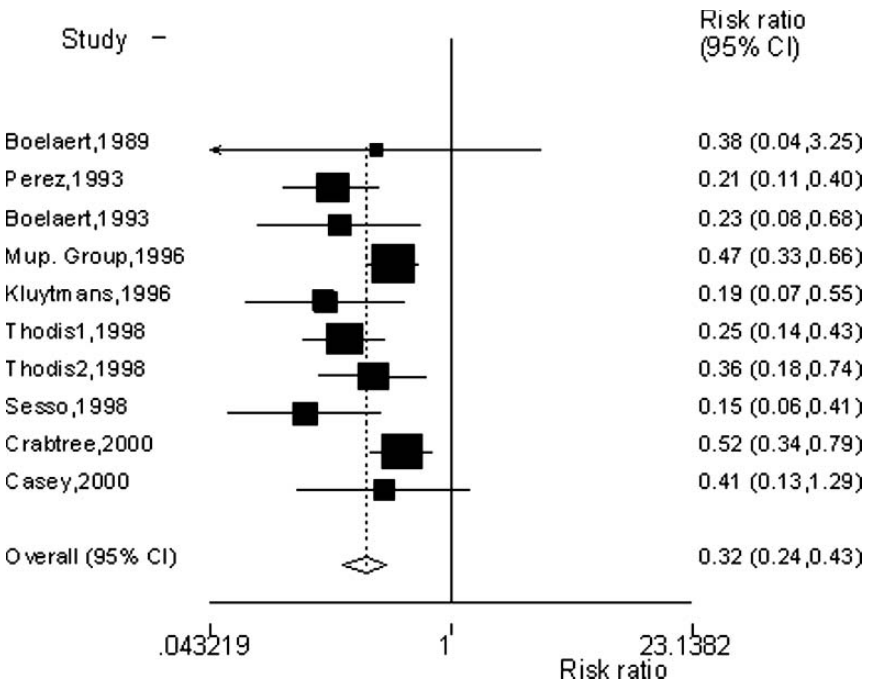



FIGURE 14.2. Risk ratio and 95% CI of *S. aureus* infections versus placebo or no prophylaxis in clinical trials for prevention of *S. aureus* infections in patients under hemodialysis or peritoneal dialysis. Adapted from Tacconelli et al. (2003).

mupirocin was generally highly effective for eradication of nasal carriage in the short term, although prophylaxis did not reduce the overall rate of infections. The authors concluded that mupirocin should be used for patients when the period of risk for infection is acute as for patients who have undergone cardiac surgery, patients with multiple trauma or severe underlying disease. A recent Cochrane systematic review, limited to patients on peritoneal dialysis, demonstrated that nasal mupirocin reduces exit-site/tunnel infection but not peritonitis (Strippoli et al. 2004).

Nevertheless, the optimal strategy for the use of mupirocin in preventing *S. aureus* colonization and infection and minimizing the emergence of resistance is still unclear. Since patients often become recolonized with *S. aureus* after an initial treatment, periodic screening of high-risk patients with application of mupirocin among carriers seems to be a reasonable option. This strategy would limit any unnecessary use, thereby decreasing the emergence of resistance.

## Risk Assessment for Mortality Caused by MRSA

The debate about the risk of excess mortality caused by MRSA is still open. The majority of the studies demonstrated that MRSA infections are significantly associated with longer hospitalization, more days of antibiotic treatment, and

higher costs when compared to MSSA infections (Osmon et al. 2004, Cosgrove et al. 2005). In a cohort study of 348 patients with MRSA (96 patients) or MSSA bacteremia (252 patients) methicillin resistance was associated with significant increases in length of hospitalization and hospital charges. MRSA bacteremia had a median attributable duration of hospitalization of 2 days and a median attributable hospital charge of 6916 dollars (Cosgrove et al. 2005).

In a prospective cohort study, Melzer and colleagues (2003) observed that patients with MRSA bacteremia were older and had more frequent ICU admissions and wounds. After adjusting for confounders (except for the appropriateness of initial empirical antibiotic therapy), attributable mortality was significantly higher in bacteremic MRSA patients than in MSSA patients. On the contrary, a recent paper (Buck et al. 2005) observed that MRSA was not an independent risk factor for mortality in ICU patients with ventilator-associated pneumonia (VAP). The authors compared VAP cases caused by MRSA with those caused by MSSA stratified by initial ICU therapy, length of hospitalization, and patients' characteristics and found that methicillin resistance did not affect hospital mortality rate.

In a meta-analysis comparing the risk of death from bacteremia caused by MRSA and MSSA, Whitby and co-workers (2001) demonstrated that MRSA bacteremia was associated with a summary relative risk of death of 2.12. Cosgrove and colleagues (2003) performed a meta-analysis of 31 studies on *S. aureus* bacteremia published between January 1980 and December 2000. Presence of heterogeneity was studied with a subgroup analysis including analysis of attributable mortality, risk adjustment, presence or absence of outbreak, inclusion of more or less than 40% of CVC-related infections, and more or less than 45% of cases of endocarditis. Analyzing only the 11 studies adjusted for confounders, the authors found that mortality was higher among patients with MRSA compared to patients with MSSA bacteremia.

Potential reasons for a worse outcome may be related to a possible enhanced virulence of MRSA versus MSSA, delay in appropriate antibiotic therapy, and decreased effectiveness of vancomycin. Although there is no evidence to suggest MRSA strains are more virulent than MSSA strains, some reports suggested that vancomycin may be an inferior antistaphylococcal treatment compared with penicillase resistant penicillins (Small and Chambers 1990, Levine et al. 1991).

Compared to MSSA, MRSA bacteremia seems to be associated with a worse outcome. Differences in studies results might be related to different patient populations, severity of underlying diseases, empiric treatment used, and source of bacteremia. Therefore, in hospitals where MRSA is endemic, empiric therapy, in patients with high suspicion of bacteremia, should include coverage for MRSA.

## Comments

Preventing transmission of methicillin-resistant *S. aureus* is important since these infections are associated with considerable morbidity and mortality, and excess hospital costs. Rising rates of methicillin-resistant staphylococcal infections also

result in a greater use of vancomycin with an increased risk of emergence of glycopeptide-resistant pathogens. Knowing variables identifying patients at higher risk for being carriers or infected with MRSA may assist clinicians in targeting preventive measures and streamlining vancomycin use.

Up to now the majority of the prevention strategies in hospitals have targeted the middle component of the endemic state: cross-transmission among hospitalized patients. Many researches have showed the importance of the influx of antibiotic bacteria into the hospitals. Epidemiological studies are therefore necessary to understand variables associated with high risk of being colonized or infected with antibiotic-resistant bacteria at hospital admission. In particular, the clinical prediction rules elaborated for MRSA and VRE provide an additional strategy by targeting the influx of the microorganism into the hospital and identifying patients harboring MRSA and VRE at hospital admission. This strategy could be used to limit the potential for MRSA dissemination from these unrecognized reservoirs from the start of their hospitalisation, as opposed to other strategies, in which screening programs target patients already hospitalized. Although the influx of antibiotic resistant microorganism into the hospital would not change, the benefit of early detection is obvious by reducing the time these patients might have to disseminate MRSA.

The spread of antibiotic-resistant infections inside the hospital is a complex mechanism. Meticulous attention to infection-control practice remains of paramount importance in preventing the dissemination of MRSA inside hospitals worldwide. Elucidating and intervening on all the components of the transmission chain may allow the acquisition of more weapons to win this fight.

## *References*

Biedenbach DJ, Moet GJ, Jones RN (2004) Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). Diagn Microbiol Infect Dis 50(1):59–69.

Buck JM, Como-Sabetti K, Harriman KH, Danila RN, Boxrud DJ, Glennen A, Lynfield R (2005) Community-associated methicillin-resistant Staphylococcus aureus, Minnesota, 2000–2003. Emerg Infect Dis 11:1532–8

Calfee DP, Durbin LJ, Germanson TP, Toney DM, Smith EB, Farr BM (2003) Spread of methicillin-resistant Staphylococcus aureus (MRSA) among household contacts of individuals with nosocomially acquired MRSA. Infect Control Hosp Epidemiol 24:422–6.

Campbell AL, Bryant KA, Stover B, Marshall GS (2003) Epidemiology of methicillin-resistant Staphylococcus aureus at a children's hospital. Infect Control Hosp Epidemiol 24:427–30.

CDC NNIS System (2003) National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 31:481–98.

Centers for Disease Control and Prevention (2002) *Staphylococcus aureus* resistant to vancomycin—United States, 2002. MMWR 51:565–7.

Charlebois E D, Bangsberg DR, Moss NJ, Moore MR, Moss AR, Chambers HF, Perdreau-Remington F (2002) Population-based community prevalence of methicillin-resistant *Staphylococcus aureus* in the urban poor of San Francisco. Clin Infect Dis 34:425–33.

Chow JW, Yu VL (1989) Staphylococcus aureus nasal carriage in hemodialysis patients. Its role in infection and approaches to prophylaxis. Arch Intern Med 149:1258–62.

Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: A meta-analysis. Clin Infect Dis 36:53–9.

Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y (2005) The impact of methicillin resistance in Staphylococcus aureus bacteremia on patient outcomes: Mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 26:166–74.

D'Agata EM, Horn MA, Webb GF (2002) The impact of persistent gastrointestinal colonization on the transmission dynamics of vancomycin-resistant enterococci. J Infect Dis 185:766–73.

Eveillard M, Ernst C, Cuviller S, Lescure FX, Malpaux M, Defouilloy I, Gresanleux M, Duboisset M, Lienard J, Eb F (2002) Prevalence of methicillin-resistant *Staphylococcus aureus* carriage at the time of admission in two acute geriatric wards. J Hosp Infect 50:122–6.

Eveillard M, Lancien E, Barnaud G, Hidri N, Gaba S, Benlolo JA, Joly-Guillou ML (2005) Impact of screening for MRSA carriers at hospital admission on risk-adjusted indicators according to the imported MRSA colonization pressure. J Hosp Infect 59:254–8.

Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ (2002) Health care-associated bloodstream infections in adults: A reason to change the accepted definition of community-acquired infections. Ann Intern Med 137:791–7.

Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, Harriman K, Harrison LH, Lynfield R, Farley MM (2005) Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 352:1436–44.

Furuno JP, Harris AD, Wright MO, McGregor JC, Venezia RA, Zhu J, Perencevich EN (2004) Prediction rules to identify patients with methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci upon hospital admission. Am J Infect Control 32:436–40.

Furuno JP, Perencevich EN, Johnson JA, Wright MO, McGregor JC, Morris JG, Strauss SM, Roghman MC, Nemoy LL, Standiford H, Hebden JN, Harris AD (2005) Methicillin-resistant Staphylococcus aureus and vancomycin-resistant co-colonisation. Emerg Infect Dis 11: 1539–44.

Garrouste-Orgeas M, Timsit JF, Kallel H, Ben Ali A, Dumay MF, Paoli B, Misset B, Carlet J (2001) Colonization with methicillin-resistant Staphylococcus aureus in ICU patients: Morbidity, mortality, and glycopeptide use. Infect Control Hosp Epidemiol 22:687–92.

Graffunder EM, Venezia RA (2002) Risk factors associated with nosocomial methicillin- resistant Staphylococcus aureus (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother 49:999–1005.

Grundmann H, Hori S, Winter B, Tami A, Austin DJ(2002) Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: Fitting a model to the data. J Infect Dis 185:481–8.

Ho PL; For the Hong Kong intensive care unit antimicrobial resistance study (HK-ICARE) Group (2003) Carriage of methicillin-resistant Staphylococcus aureus, ceftazidime-resistant Gram-negative bacilli, and vancomycin-resistant enterococci before and after intensive care unit admission. Crit Care Med 31:1175–82.

Huang SS, Labus BJ, Samuel MC, Wan DT, Reingold AL (2002) Antibiotic resistance patterns of bacterial isolates from blood in San Francisco County, California, 1996–1999. Emerg Infect Dis 8:195–201.

Huang SS, Platt R (2003) Risk of methicillin-resistant Staphylococcus aureus infection after previous infection or colonization. Clin Infect Dis 36:281–5.

Kenner J, O'Connor T, Piantanida N, Fishbain J, Eberly B, Viscount H, Uyehara C, Hospenthal D (2003) Rates of carriage of methicillin-resistant and methicillin-susceptible Staphylococcus aureus in an outpatient population. Infect Control Hosp Epidemiol 24:439–44.

Laupland KB, Conly JM (2003) Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: An evidence-based review. Clin Infect Dis 37:933–8.

Levine DP, Fromm BS, Reddy BR (1991) Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. Ann Intern Med 115:674–80.

Lucet JC, Chevret S, Durand-Zaleski I, Chastang C, Regnier B; Multicenter Study Group (2003) Prevalence and risk factors for carriage of methicillin-resistant Staphylococcus aureus at admission to the intensive care unit: Results of a multicenter study. Arch Intern Med 163:181–8.

Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR (1999) Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 20:250–78.

Melzer M, Eykyn SJ, Gransden WR, Chinn S (2003) Is methicillin-resistant Staphylococcus aureus more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis 37:1453–60.

Mest DR, Wong DH, Shimoda KJ, Mulligan ME, Wilson SE (1994) Nasal colonization with methicillin-resistant Staphylococcus aureus on admission to the surgical intensive care unit increases the risk of infection. Anesth Analg 78:644–50.

Miller MA, Dascal A, Portnoy J, Mendelson J (1996) Development of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* after widespread use of nasal mupirocin ointment. Infect Control Hosp Epidemiol 17:811–3.

Onorato M, Borucki MJ, Baillargeon G, Paar DP, Freeman DH, Cole CP, Mayhall CG (1999) Risk factors for colonization or infection due to methicillin-resistant Staphylococcus aureus in HIV-positive patients: A retrospective case–control study. Infect Control Hosp Epidemiol 20:26–30.

Osmon S, Ward S, Fraser VJ, Kollef MH (2004) Hospital mortality for patients with bacteremia due to Staphylococcus aureus or Pseudomonas aeruginosa. Chest 125:607–16.

Papia G, Louie M, Tralla A, Johnson C, Collins V, Simor AE (1999) Screening high-risk patients for methicillin-resistant Staphylococcus aureus on admission to the hospital: Is it cost effective? Infect Control Hosp Epidemiol 20:473–7.

Paterson DL, Rihs JD, Squier C, Gayowski T, Sagnimeni A, Singh N (2003) Lack of efficacy of mupirocin in the prevention of infections with Staphylococcus aureus in liver transplant recipients and candidates. Transplantation 75:194–8.

Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, Twombley J, French PP, Herwaldt LA (2002) Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. New Engl J Med 346:1871–7.

Rezende NA, Blumberg HM, Metzger BS, Larsen NM, Ray SM, McGowan JE Jr (2002) Risk factors for methicillin-resistance among patients with Staphylococcus aureus bacteremia at the time of hospital admission. Am J Med Sci 323:117–23.

Rubinovitch B, Pittet D (2001) Screening for methicillin-resistant *Staphylococcus aureus* in the endemic hospital: What have we learned? J Hosp Infect 47:9–18.

Salgado CD, Farr BM, Calfee DP (2003) Community-acquired methicillin-resistant *Staphylococcus aureus*: A meta-analysis of prevalence and risk factors. Clin Infect Dis 36:131–9.

Sax H, Harbarth S, Gavazzi G, Henry N, Schrenzel J, Rohner P, Michel JP, Pittet D (2005) Prevalence and prediction of previously unknown MRSA carriage on admission to a geriatric hospital. Age Ageing 34:456–62.

Scarnato F, Mallaret MR, Croize J, Kouabenan DR, Dubois M, Maitre A, DeGaudemaris R (2003) Incidence and prevalence of methicillin-resistant Staphylococcus aureus nasal carriage among healthcare workers in geriatric departments: Relevance to preventive measures. Infect Control Hosp Epidemiol 24:456–8.

Schelenz S, Tucker D, Georgeu C, Daly S, Hill M, Roxburgh J, French GL (2005) Significant reduction of endemic MRSA acquisition and infection in cardiothoracic patients by means of an enhanced targeted infection control programme. J Hosp Infect 60:104–10.

Small PM, Chambers HF (1990) Vancomycin for Staphylococcus aureus endocarditis in intravenous drug users. Antimicrob Agents Chemother 34:1227–31.

Strippoli GF, Tong A, Johnson D, Schena FP, Craig JC (2004) Antimicrobial agents for preventing peritonitis in peritoneal dialysis patients. Cochrane Database Syst Rev Oct 18;(4):CD004679.

Suzuki Y, Kamigaki T, Fujino Y, Tominaga M, Ku Y, Kuroda Y (2003) Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery. Br J Surg 90:1072–5.

Tacconelli E, Carmeli Y, Aizer A, Ferreira G, Foreman MG, D'Agata EM (2003a) Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: A meta-analysis. Clin Infect Dis 37:1629–38.

Tacconelli E, D'Agata EM, Karchmer AW (2003b) Epidemiological comparison of true methicillin-resistant and methicillin-susceptible coagulase-negative staphylococcal bacteremia at hospital admission. Clin Infect Dis 37:644–9.

Tacconelli E, Karchmer AW, Yokoe D, D'Agata EM (2004a) Preventing the influx of vancomycin-resistant enterococci into health care institutions, by use of a simple validated prediction rule. Clin Infect Dis 39:964–70.

Tacconelli E, Venkataraman L, De Girolami PC, DAgata EM (2004b) Methicillin-resistant Staphylococcus aureus bacteraemia diagnosed at hospital admission: Distinguishing between community-acquired versus healthcare-associated strains. J Antimicrob Chemother 53:474–9.

Tsiodras S, Gold S, Sakoulas G, Eliopoulos GM, Wennersten C, Venkataraman L, Moellering RC, Ferraro MJ (2001) Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. Lancet 358:207–8.

Tumbarello M, de Gaetano Donati K, Tacconelli E, Citton R, Spanu T, Leone F, Fadda G, Cauda R (2002) Risk factors and predictors of mortality of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in HIV-infected patients. J Antimicrob Chemother 50:375–82.

Weber JT (2005) Community-associated methicillin-resistant Staphylococcus aureus. Clin Infect Dis 41 (Suppl 4): 269–72.

Weber SG, Gold HS, Hooper DC, Karchmer AW, Carmeli Y (2003) Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis 9:1415–22.

Wilcox MH, Hall J, Pike H, Templeton PA, Fawley WN, Parnell P, Verity P (2003) Use of perioperative mupirocin to prevent methicillin-resistant Staphylococcus aureus (MRSA) orthopaedic surgical site infections. J Hosp Infect 54:196–201.

Whitby M, McLaws ML, Berry G (2001) Risk of death from methicillin-resistant Staphylococcus aureus bacteraemia: A meta-analysis. Med J Aust 175:264–7.

Working Party Report (1998) Revised guidelines for the control of methicillin-resistant Staphylococcus aureus infection in hospitals. British Society for Antimicrobial Chemotherapy, Hospital Infection Society and the Infection Control Nurses Association. J Hosp Infect 39:253–90.

Zhan C, Miller MR (2003) Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. JAMA 290:1868–74.

# Chapter 15
# What Do We Do with Methicillin-Resistant *Staphylococcus aureus* in Surgery?

Giorgio Zanetti

Methicillin-resistant *Staphylococcus aureus* (MRSA) is typical of the burden of antimicrobial resistance in nosocomial infections. *S. aureus* is one of the most frequent nosocomial pathogens, and the prevalence of methicillin resistance has been constantly rising among *S. aureus* strains over the last four decades. This has been responsible for an increase in length of hospital stay, treatment-related complications, costs, and, in some instances, attributable mortality.

Because MRSA, like methicillin-susceptible *S. aureus* (MSSA), frequently colonizes the skin, it is of particular concern as a cause of infection in surgical patients. However, the antibiotics commonly recommended for perioperative prophylaxis do not target MRSA. Therefore, one can legitimately wonder if current preventive measures are still sufficient.

## Epidemiology of MRSA: Trends Relevant to Surgical Patients

Methicillin-resistant strains of *S. aureus* were first isolated in the 1960s, shortly after the introduction of methicillin (Jevons et al. 1963). In the 1970s and 1980s, the epidemiology of MRSA infections was characterized by small outbreaks that could be controlled by standard measures. A decade later, strains emerged that became endemic in many hospitals.

Methicillin resistance is characterized by wide geographical variations. In Europe, the prevalence of resistance to methicillin in *S. aureus* isolated from blood varies almost 100-fold, from $<1\%$ in northern countries to $>40\%$ in southern and western countries (The European Antimicrobial Resistance Surveillance System [EARSS] 2004). In addition, this prevalence differs notably among hospitals within countries, the highest variance being observed in countries with a prevalence of 5 to 20% (Tiemersma et al. 2004). In the United States, MRSA accounted for nearly 60% of nosocomial *S. aureus* infections acquired in intensive care units in 2002 (Anonymous 2004). This proportion peaks in Japan, where MRSA was responsible for nearly 70% of *S. aureus* bloodstream infections in 2001 (Boyce et al. 2005).

The prevalence of MRSA is escalating almost everywhere since 1990, and particularly since 2000 (Biedenbach et al. 2004). In EARSS, for instance, a rise was observed in 13 of 19 participating countries, although this trend was significant in only 5 of them (Tiemersma et al. 2004).

New MRSA strains have emerged *de novo* from community-based *S. aureus*. These Community-acquired MRSA (CA-MRSA) strains are frequently associated with skin infections, particularly in children, and tend to be susceptible to more antibiotics than healthcare-associated MRSA (Fridkin et al. 2005). A relatively small number of unique strains appear to be involved. They are genetically distinct from healthcare-associated strains. Most contain the mobile genetic element staphylococcal cassette chromosome *mec* type IV, which is uncommon among healthcare-associated MRSA (Boyce et al. 2005).

Although CA-MRSA infections have been more common among population groups such as young children, native American, and Pacific Islander communities, prisoners, military personnel, men who have sex with men, intravenous drug users, and individuals involved in competitive sports, spread within the general community is likely occurring simultaneously in several places in the world. These new strains jeopardize the well-established strategies to control nosocomial MRSA in countries with low prevalence, like Finland, the Netherlands, and Denmark. Denmark, for instance, experienced a marked increase in MRSA since 2004 due to the epidemic spread of CA-MRSA (Faria et al. 2005).

## Risk Factors for MRSA Infection in Surgical Patients

The main and most frequently reported risk factors for colonization with or infection by MRSA in all hospitalized patients include a history of previous MRSA colonization or infection, previous hospital stay, the length of the current hospital stay, the presence of invasive devices, previous antibiotic treatments, contact with a roommate who carries MRSA, chronic skin ulcers, and diabetes mellitus (Graffunder and Venezi 2002, Tacconelli et al. 2004, Troillet et al. 1998). In addition, belonging to specific patient populations (e.g. intravenous drug users, nursing home residents) may be predictive of MRSA carriage in some regions as a consequence of local epidemic situations.

Dodds Ashley et al. undertook a case–control study comparing 64 patients who developed an MRSA mediastinitis after a median sternotomy to 79 patients with mediastinitis due to MSSA and 80 uninfected control patients (Dodds Ashley et al. 2004). In a multivariate analysis, patients who were diabetic, female, and $>$70 years old were more likely to develop mediastinitis due to MRSA, with adjusted ORs of 2.86, 2.70, and 3.43, respectively. Only obesity was a risk factor for MSSA mediastinitis.

Some postoperative factors may also play a role. In a retrospective study of 270 microbiologically documented SSI, MRSA infection was independently associated with discharge to a long-term care facility and duration of postoperative antibiotic treatment of $>$1 day (Manian et al. 2003).

## Physiopathology of MRSA Infections in Surgical Patients

MRSA and MSSA infections share common pathogenic mechanisms. Although asymptomatic nasal colonization with *S. aureus* is common, it appears to be an important factor in the development of most infections due to this organism (von Eiff et al. 2001).

Binding of *S. aureus* cell-surface components (e.g., teichoic acids) with either carbohydrate-rich surface components of mucosal epithelial cells or nasal mucus secretions provides a suitable explanation for initial colonization. Long-term carriage, however, is less understood. Inverted confocal laser scan fluorescence and electron microscopic examination of intranasal biopsy specimens from patients suffering from recurrent *S. aureus* rhinosinusitis revealed foci of intracellular reservoirs of *S. aureus* in the epithelium, glandular, and myofibroblastic cells (Clement et al. 2005).

Of 450 university student volunteers from North Carolina, 29% were *S. aureus* carriers. Two percent of the *S. aureus* were resistant to methicillin. Independent risk factors for carriage in this setting included older age, male gender, and chronic sinusitis (Bischoff et al. 2004). Carriage is most often clonal, although one observation suggested that about 7% of *S. aureus*-colonized individuals carry more than one strain (Cespedes et al. 2005).

Conflicting results have been published on risk factors for nasal carriage in patients. In the context of a clinical trial evaluating whether mupirocin prevented surgical site infections due to *S. aureus*, Herwaldt et al. prospectively collected data on 70 characteristics in a population of 4030 patients before surgery. Twenty-two percent of these patients carried *S. aureus* in their nares; the proportion of MRSA was not specified. Independent risk factors for *S. aureus* nasal carriage were obesity, male gender, and a history of cerebrovascular accident (Herwaldt et al. 2004).

An illustration of the relationship between *S. aureus* carriage and the subsequent occurrence of *S. aureus* infection was published by Wertheim et al. (2004). They screened 14,008 nonsurgical patients at hospital admission for *S. aureus* nasal carriage, and monitored them for development of bacteremia. Nosocomial *S. aureus* bacteremia was three times more frequent in *S. aureus* carriers (1.2%) than in noncarriers (0.4%), a significant increase (95% CI for the relative risk: 2.0–4.7). Eighty percent of the strains that caused bacteremia in carriers were endogenous.

The role of *S. aureus* carriage was also observed in the surgical setting. Numerous studies have shown that surgical patients who carry *S. aureus* in their anterior nares were at increased risk for *S. aureus* surgical site infections (SSIs), and that those infections are usually caused by the same strains that were carried by these patients prior to surgery (Herwaldt 2003).

## Burden of MRSA Infection in Surgical Patients

The burden of MRSA infection can be inferred from two distinct perspectives. Some studies describe it as a part of all *S. aureus* infections. Their results are instructive but poorly generalizable because this part varies from

one hospital to the other. Other studies describe the burden of MRSA through comparison with MSSA.

*S. aureus* has consistently been reported as the most frequent cause of infections at surgical sites (Jernigan 2004). According to NNISS data, for instance, 30.9% of SSIs following CABG, cholecystectomy, colectomy, and total hip replacement were due to *S. aureus*; the proportion of *S. aureus* infections attributable to MRSA increased from 9.2% in 1992 to 49.3% in 2002 (Anonymous 2004). In another study, *S. aureus* accounted for 49% of sternal SSI developing after CABG (Sharma et al. 2004). Thirty-six percent of these *S. aureus* were MRSA. Bacteremia was noted in 31.4% of patients with sternal SSI, and all were due to *S. aureus*. The most devastating infectious complication of cardiothoracic surgery is mediastinitis, which occurs in 1 to 4% of patients (Dodds Ashley et al. 2004) and entails a mortality rate of 10–47% (Abboud et al. 2004). MRSA has been a common cause, accounting for as many as 65% of cases (Lin et al. 2003).

*S. aureus* SSI has been independently associated with increased mortality, length of stay, and cost (McGarry et al. 2004). There is substantial evidence suggesting that methicillin resistance further affects the prognosis but this is still debated. This was not the case in one study on short-term (ICU) mortality among patients with posternotomy mediastinitis due to *S. aureus* (Combes et al. 2004). Conflicting results were published, however, showing that MRSA SSI may be associated with a higher mortality rate than MSSA SSI (Engemann et al. 2003, Mekontso-Dessap et al. 2001). For instance, in the study by Engemann et al. (2003), 20.7% of patients with MRSA SSI died during the 90-day postoperative period, compared with 6.7% of patients with SSI caused by MSSA (adjusted OR 3.4, 95% CI 1.5–7.2). Besides SSI, data suggest that methicillin resistance may be associated with an increase in mortality of *S. aureus* bacteremia. In a prospective study of 815 patients with nosocomial *S. aureus* bacteremia, there was a trend toward higher attributable mortality in patients with MRSA bacteremia compared with MSSA (OR 1.72 after adjustment for host variables, 95% CI 0.92–3.20) (Melzer et al. 2003). In a meta-analysis of 31 published studies, Cosgrove et al. confirmed that methicillin resistance was associated with an increased mortality in case of *S. aureus* bacteremia (pooled OR 1.93, 95% CI 1.54–2.42) (Cosgrove et al. 2003).

Even if a higher virulence of MRSA compared with MSSA were to be confirmed, there would be uncertainty regarding its cause. A worse prognosis of MRSA infections could indeed be due to the pathogen itself or to suboptimal antistaphylococcal activity of vancomycin compared with β-lactam antibiotics (Jernigan 2004).

## Prevention

Preventive measures discussed below have different goals. Prophylactic use of topical and/or systemic antibiotics aims at preventing MRSA from causing SSI in MRSA carriers. One may consider this use either in the whole population of

surgical patients or in patients targeted for presumed or proven colonization with MRSA. However, its impact is not well established yet. Infection control precautions aim at preventing transmission of MRSA to noncolonized patients. Finally, antibiotic policies might be beneficial with respect to these two aspects, i.e., the risk that colonized patients will develop an MRSA infection and the risk that uncolonized patients will acquire an MRSA strain.

## *Preoperative Use of Topical Antibiotics Active Against MRSA*

The impact of topical antibiotic for eradication of MSSA and/or MRSA is best known for mupirocin, a compound synthesized by *Pseudomonas fluorescens* that inhibits bacterial protein synthesis by reversibly binding to bacterial isoleucyl-tRNA synthetase. Several studies have demonstrated the efficacy of mupirocin for the eradication of MRSA and MSSA in different populations (Laupland and Colby 2003). Its effect in healthy healthcare workers (Doebbeling et al. 1993, Fernandez et al. 1995, Reagan et al. 1991, Scully et al. 1992) may be particularly relevant for prevention in surgical patients. By pooling six double-blind, randomized studies in 339 healthcare workers who carried *S. aureus* in their nose, Doebbeling et al. reported that the application of mupirocin twice daily for 5 days eradicated 91% of participants, compared with 6% of those who received a placebo. No emergence of resistance to mupirocin was observed (Doebbeling et al. 1993).

Early studies in the surgical setting were promising, showing not only decolonization, but also significantly lower SSI rates among patients who received preoperative intranasal mupirocin treatment compared with historical controls (Cimochowski et al. 2001, Gernaat-van der Sluis et al. 1998, Kluytmans et al. 1996). More recently, Perl et al. published a double-blind, randomized, placebo-controlled trial that included 4030 patients who underwent general, gynecologic, neurological, or cardiothoracic surgery (Perl et al. 2002). Mupirocin was administered intranasally twice per day for up to 5 days before surgery. The rate of *S. aureus* SSI in mupirocin recipients (2.3%) was not significantly different from that in placebo recipients (2.4%). However, in the secondary analysis of 891 nasal carriers of *S. aureus* (22%, proportion of MRSA not reported), significantly fewer mupirocin-treated patients developed surgical and nonsurgical nosocomial *S. aureus* infections (4%) compared with patients who received placebo (7.7%). This reduction was significant (OR for infection 0.49, 95%CI 0.25–0.92). Mupirocin was also more frequently associated with decolonization (84% versus 27%) although only 83% of the patients received three doses or more. The rate of resistance to mupirocin was low (0.6% of 1021 isolates).

A smaller double blind, randomized, placebo-controlled trial was conducted in 614 patients undergoing elective orthopedic surgery with insertion of implant material (Kalmeijer et al. 2002). Mupirocin or placebo was given intranasally twice a day the day before surgery and the day of surgery. As in Perl's study, *S. aureus* SSI rates were similar in the mupirocin group (3.8%) and the placebo group (4.7%) despite a higher eradication rate with mupirocin (84%, compared

with 22% in placebo recipients). Furthermore, the incidence of *S. aureus* SSIs was similar in both groups.

In conclusion, data available to date do not support routine administration of prophylactic intranasal mupirocin to prevent SSI. Subgroup analyses have suggested a small reduction of *S. aureus* infections—thus presumably of MRSA infections as well—in patients who carry this bacterium. This benefit, which still needs confirmation, would require the identification of MRSA carriers, a topic that will be addressed below in the section on infection control measures.

## *Systemic Perioperative Prophylaxis with Antibiotic Active Against MRSA*

The impact of perioperative antibiotic prophylaxis on SSI due to staphylococci has been mainly studied in patients undergoing cardiac surgery. SSI is indeed a frequent complication of cardiac surgery. The most severe SSIs, deep sternal wound infection and mediastinitis, occur in 0.25 to 2% of the patients. They often require reoperation and prolonged antibiotic therapy, and are associated with mortality rates of up to 30%. Guidelines typically recommend antibiotic prophylaxis with a first- or second-generation cephalosporin, based on many clinical studies conducted before the 1990s that have been summarized in a meta-analysis published in 1992 (Kreter and Woods 1992).

The use of a cephalosporin is frequently challenged because of the escalating prevalence of resistance to methicillin in Gram-positive cocci that are responsible for SSI after cardiac surgery. *S. aureus* and coagulase-negative staphylococci indeed account for 34–54% and 12–44% of these infections, respectively (Borger et al. 1998, Grossi et al. 1985, Munoz et al. 1997), and resistance to methicillin was found in 41% of *S. aureus* isolates and 64% of *Staphylococcus epidermidis* isolates responsible for nosocomial infections in the U.S. National Nosocomial Infections Surveillance between 1992 and 2002 (Anonymous 2002).

For this reason, glycopeptides (vancomycin or teicoplanin) are often used for cardiac surgery prophylaxis. However, the debate about glycopeptide prophylaxis is lively because of the concern that use of these agents may promote the emergence and the spread of resistance to this family of antibiotics among enterococci and staphylococci. The Centers for Disease Control and Prevention recommends that vancomycin only be used as perioperative prophylaxis "at institutions that have a high rate of infections caused by MRSA or methicillin-resistant *S. epidermidis*" (Anonymous 1995, Bratzler and Houck 2004). However, this recommendation provides no guidance about what rate is sufficiently high to warrant use of a glycopeptide. The amount of glycopeptide use at stake is all the larger as these considerations apply to many clean surgical procedures (Zanetti and Platt 2004).

Bolon et al. (2004) published a meta-analysis of seven randomized trials that compared SSIs in cardiac surgery patients receiving prophylaxis with either a glycopeptide or a β-lactam (Table 15.1). Neither agent proved to be superior for prevention of SSI. In subgroup analysis, β-lactam prophylaxis prevented 50% more chest SSIs than did glycopeptide prophylaxis, a difference that might be

TABLE 15.1. Clinical trials comparing glycopeptides and β-lactam antibiotics for prophylaxis of surgical site infections (SSI) after cardiothoracic surgery

| Authors | Blinded | Glycopeptide [No SSI/No patients (%)] | β-Lactam [No SSI/No patients (%)] | Relative risk with glycopeptide (95% CI) | Prevalence of MRSA[a] |
|---|---|---|---|---|---|
| Wilson et al. (1988) (trial 1) | No | Teicoplanin [20/149 (13.4)] | Flucloxacillin – tobramycin [10/165 (6.1)] | 2.2 (1.0–4.7) | Low[b] |
| Wilson et al. (1988) (trial 2) | No | Teicoplanin [12/139 (8.6)] | Flucloxacillin – tobramycin [4/64 (6.3)] | 1.3 (0.5–4.3) | Low[b] |
| Maki et al. (1992) | Yes | Vancomycin [2/78 (2.6)] | Cefazolin or cefamandole [16/170 (9.4)] | 0.3 (0.1–1.2) | Low[b] |
| Vuorisalo et al. (1998) | No | Vancomycin [15/440 (3.4)] | Cefuroxime [14/444 (3.2)] | 1.1 (0.5–2.2) | Low |
| Salminen et al. (1999) | No | Vancomycin [6/103 (5.8)] | Ceftriaxone [5/97 (5.2)] | 1.1 (0.3–3.7) | Low[b] |
| Saginur et al. (2000) | Yes | Teicoplanin [174/1518 (11.5)] | Cefazolin [155/1509 (10.3)] | 1.1 (0.9–1.4) | Low |
| Finkelstein et al. (2002) | No | Vancomycin [43/452 (9.5)] | Cefazolin [39/433 (9)] | 1.1 (0.7–1.6) | High |

[a] No quantitative data available.
[b] From Bolon et al. (2004).

explained by poorer penetration of glycopeptides into sternal bone and fatty tissue, and by the slow killing rate of these antibiotics at the achieved concentrations. The authors concluded that standard prophylaxis for cardiac surgery should continue to be β-lactams in most circumstances. Similar conclusions were drawn in a meta-analysis of teicoplanin compared to first- or second-generation cephalosporins for prophylaxis in orthopedic and vascular surgery involving prosthetic material (Vardakas et al. 2005).

However, the risk of SSI caused by methicillin-resistant, Gram-positive organisms in patients who received prophylaxis with a glycopeptide was one-half of that observed for patients who received β-lactam antibiotics in the meta-analysis of studies in cardiac surgery (Bolon et al. 2004). Local prevalence of methicillin resistance will therefore be a key factor in the choice of a prophylactic strategy. Unfortunately, available studies did not precisely specify this prevalence. Most of them included patients during the 1980s or early 1990s, and are therefore unlikely to reflect the current situation of methicillin resistance. Only the most recent study, which was conducted in Israel during 1997–1999, describes a high prevalence of MRSA without specifying what this prevalence was. Of note, no advantage of vancomycin prophylaxis was found overall, even in this study. Therefore, the question of a threshold value for prevalence of methicillin resistance that would justify prophylaxis with glycopeptides remains unanswered.

The potential for promoting the emergence of resistance by using glycopeptides is obvious. Most of the patients reported with glycopeptide-resistant or intermediate *Staphylococcus aureus* had previously received prolonged courses of vancomycin for infections caused by MRSA (Hiramatsu et al. 1997, Smith et al. 1999). However, epidemiological data are still too conflicting to translate this paradigm into clinical practice. For instance, vancomycin has been less consistently reported as a risk factor for infections caused by vancomycin-resistant enterococci than cephalosporins (Martone 1998). In addition, short exposures to glycopeptides for prophylaxis in non-MRSA patients are far less likely to promote resistance than prolonged treatments, especially for MRSA infections. We recently developed a decision-analytic model to calculate the clinical benefits and costs associated with the use of either cefazolin or vancomycin for prophylaxis in coronary artery bypass surgery (Zanetti et al. 2001). In the base case, where 40% of *S. aureus* and 80% of coagulase-negative staphylococci were resistant to methicillin, cefazolin had to be 25% better than vancomycin against susceptible organisms in order to be more effective. A performance advantage for cefazolin against susceptible organisms was required unless the prevalence of methicillin resistance was less than 3%. This example illustrates the uncertainty concerning the effects of vancomycin prophylaxis: choosing cefazolin over vancomycin for cardiac surgery may be detrimental to the individual patient in many hospitals.

At this point, it can be concluded that there is no empirical evidence supporting a switch from β-lactam to glycopeptides for routine prophylaxis in patients undergoing cardiac surgery—a conclusion that may be extrapolated to other types of clean surgery. However, more data are warranted to help clinicians make the best choice based on the most common pathogens at each institution (Zanetti and Platt 2004).

The decision to choose an antibiotic prophylaxis that covers MRSA in individual patients who carry this bacterium is more obvious, since one of the principles of antibiotic prophylaxis in surgery is protection against skin colonizers. This again requires an efficient strategy to identify MRSA carriers (see below).

## *Infection Control Measures*

Colonized and infected patients represent the main reservoir of MRSA in hospitals. Healthcare workers may carry MRSA, although most often transiently. More importantly, healthcare workers may transmit the bacterium from one patient to the other on their contaminated hands or clothes. Transmission also occurs through contamination of the environment or the equipment. Infection control measures are therefore pivotal in preventing hospital transmission of MRSA. This implies a strict application of standard precautions, especially hand hygiene. Additional measures are recommended in MRSA-positive patients and typically include contact precautions with or without isolation in individual rooms, disinfection of the environment, and decolonization protocols. These protocols have not been standardized. They most often include topical disinfection and intranasal mupirocin, and sometimes systemic antibiotics.

Although the impact from the individual components of these preventive measures has not been assessed in prospective, comparative trials, there have been numerous reports of decreases in the prevalence of MRSA after their implementation in hospitals with either epidemic or endemic MRSA (Muto et al. 2003). A critical association has been described between number of skilled healthcare workers and the effect of infection control measures (Boyce et al. 2005).

Controlling transmission of MRSA is likely to have an important preventive impact in the specific setting of surgical patients. Indeed, in the study by Perl et al. (2002), 60% of the *S. aureus* SSIs appeared not to have originated from nasal carriage by the patient, suggesting an exogenous source.

Thus, routine surveillance cultures in patients at high risk for carriage of MRSA are mandated by both the need to control transmission and the need to prevent MRSA infections in carriers (e.g., by prescribing a decolonization protocol or by choosing a perioperative antibiotic prophylaxis that covers MRSA) (Muto et al. 2003).

A history of MRSA colonization or infection and transfer from a country or a hospital with a high prevalence of MRSA are classical criteria to identify the patients who should undergo routine surveillance culture at hospital admission. There may be additional criteria depending on the local epidemiology of MRSA, which implies good knowledge of the risk factors in the patient population of a given hospital. Examples of "local" criteria include residing in a nursing home, chronic hemodialysis, invasive devices, pressure sores, diabetes, or belonging to a group of people with an ongoing MRSA epidemic (e.g., intravenous drug users). In one German hospital, the use of such criteria led to screening swabs in 1.5% of inpatients (Wernitz et al. 2005). Beyond admission criteria, screening strategies

generally include people who shared the hospital room of a patient later diagnosed with MRSA colonization or infection.

## *Policies for Appropriate Use of Antibiotics*

The appropriate use of antibiotics is of interest for the prevention of MRSA infections not only for perioperative antibiotic prophylaxis but also because antibiotic consumption in general is a major contributor to emerging bacterial resistance. Several studies indeed suggest that antibiotic consumption is a risk factor for colonization or infection by MRSA at the level of the individual patient, as well as a determinant of the epidemiology of MRSA at the collective level.

Receipt of antibiotics within the previous months predisposes the individual patient to infection with or carriage of MRSA (Hidron et al. 2005). This finding has been repeatedly reported with fluoroquinolones (Crowcroft et al. 1999, Dziekan et al. 2000, Graffunder and Venezia 2002, Harbarth et al. 2000). Weber et al. specifically designed a case–case–control study to determine whether exposure to fluoroquinolones was a risk factor for the subsequent isolation of MRSA or MSSA (Weber et al. 2003). Both levofloxacin and ciprofloxacin were independently associated with isolation of MRSA (adjusted OR 3.4, 95% CI 1.9–5.9, and 2.5, 95% CI 1.3–4.7, respectively), but not MSSA.

Duration of postoperative antibiotic treatment of $> 1$ day was an independent predictor of SSI caused by MRSA compared to SSI caused by other organisms in one study (Manian et al. 2003).

As to aggregate data at the collective level, Monnet et al. demonstrated a strong temporal relationship between antimicrobial use and the dynamic of an MRSA outbreak in an Aberdeen hospital, Scotland. Using time-series analysis, they found that the use of third-generation cephalosporins, macrolides, and fluoroquinolones predicted 90% of the monthly variation of methicillin resistance in *S. aureus* (Monnet et al. 2004). Antibiotic use was also shown to correlate with prevalence of MRSA in an endemic situation (Muller et al. 2003).

Based on these data, one can add prevention of MRSA infections to the many arguments in favor of a prudent use of antibiotics.

## *References*

Abboud CS, Wey SB, Baltar VT (2004) Risk factors for mediastinitis after cardiac surgery. Ann Thorac Surg 77:676–683.

Anonymous (1995) Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 44:1–13.

Anonymous (2002) National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 to June 2002, issued August 2002. Am J Infect Control 30:458–475.

Anonymous (2004) National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 32:470–485.

Biedenbach DJ, Moet GJ, Jones RN (2004) Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997–2002). Diagn Microbiol Infect Dis 50:59–69.

Bischoff WE, Wallis ML, Tucker KB, Reboussin BA, Sherertz RJ (2004) Staphylococcus aureus nasal carriage in a student community: Prevalence, clonal relationships, and risk factors. Infect Control Hosp Epidemiol 25:485–491.

Bolon MK, Morlote M, Weber SG, Koplan B, Carmeli Y, Wright SB (2004) Glycopeptides are no more effective than beta-lactam agents for prevention of surgical site infection after cardiac surgery: A meta-analysis. Clin Infect Dis 38:1357–1363.

Borger MA, Rao V, Weisel RD, Ivanov J, Cohen G, Scully HE, David TE (1998) Deep sternal wound infection: Risk factors and outcomes. Ann Thorac Surg 65:1050–1056.

Boyce JM, Cookson B, Christiansen K, Hori S, Vuopio-Varkila J, Kocagoz S, Oztop AY, Vandenbroucke-Grauls CM, Harbarth S, Pittet D (2005) Methicillin-resistant Staphylococcus aureus. Lancet Infect Dis 5:653–663.

Bratzler DW, Houck PM (2004) Antimicrobial prophylaxis for surgery: An advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis 38:1706–1715.

Cespedes C, Said-Salim B, Miller M, Lo SH, Kreiswirth BN, Gordon RJ, Vavagiakis P, Klein RS, Lowy FD (2005) The clonality of Staphylococcus aureus nasal carriage. J Infect Dis 191:444–452.

Cimochowski GE, Harostock MD, Brown R, Bernardi M, Alonzo N, Coyle K (2001) Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics. Ann Thorac Surg 71:1572–1578.

Clement S, Vaudaux P, Francois P, Schrenzel J, Huggler E, Kampf S, Chaponnier C, Lew D, Lacroix JS (2005) Evidence of an intracellular reservoir in the nasal mucosa of patients with recurrent Staphylococcus aureus rhinosinusitis. J Infect Dis 192:1023–1028.

Combes A, Trouillet JL, Joly-Guillou ML, Chastre J, Gibert C (2004) The impact of methicillin resistance on the outcome of poststernotomy mediastinitis due to Staphylococcus aureus. Clin Infect Dis 38:822–829.

Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: A meta-analysis. Clin Infect Dis 36:53–59.

Crowcroft NS, Ronveaux O, Monnet DL, Mertens R (1999) Methicillin-resistant Staphylococcus aureus and antimicrobial use in Belgian hospitals. Infect Control Hosp Epidemiol 20:31–36.

Dodds Ashley ES, Carroll DN, Engemann JJ, Harris AD, Fowler VG Jr, Sexton DJ, Kaye KS (2004) Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. Clin Infect Dis 38:1555–1560.

Doebbeling BN, Breneman DL, Neu HC, Aly R, Yangco BG, Holley HP Jr, Marsh RJ, Pfaller MA, McGowan JE Jr, Scully BE (1993) Elimination of Staphylococcus aureus nasal carriage in health care workers: Analysis of six clinical trials with calcium mupirocin ointment. The Mupirocin Collaborative Study Group. Clin Infect Dis 17:466–474.

Dziekan G, Hahn A, Thune K, Schwarzer G, Schafer K, Daschner FD, Grundmann H (2000) Methicillin-resistant Staphylococcus aureus in a teaching hospital: Investigation of nosocomial transmission using a matched case–control study. J Hosp Infect 46:263–270.

Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS (2003) Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis 36:592–598.

Faria NA, Oliveira DC, Westh H, Monnet DL, Larsen AR, Skov R, de Lencastre LH (2005) Epidemiology of emerging methicillin-resistant *Staphylococcus aureus* (MRSA) in Denmark: A nationwide study in a country with low prevalence of MRSA infection. J Clin Microbiol 43:1836–1842.

Fernandez C, Gaspar C, Torrellas A, Vindel A, Saez-Nieto JA, Cruzet F, Aguilar L (1995) A double-blind, randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of mupirocin calcium ointment for eliminating nasal carriage of Staphylococcus aureus among hospital personnel. J Antimicrob Chemother 35:399–408.

Finkelstein R, Rabino G, Mashiah T, Bar-El Y, Adler Z, Kertzman V, Cohen O, Milo S (2002) Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. J Thorac Cardiovasc Surg 123:326–332.

Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, Harriman K, Harrison LH, Lynfield R, Farley MM (2005) Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med 352:1436–1444.

Gernaat-van der Sluis AJ, Hoogenboom-Verdegaal AM, Edixhoven PJ, Spies-van Rooijen NH (1998) Prophylactic mupirocin could reduce orthopedic wound infections. 1,044 patients treated with mupirocin compared with 1,260 historical controls. Acta Orthop Scand 69:412–414.

Graffunder EM, Venezia RA (2002) Risk factors associated with nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother 49:999–1005.

Grossi EA, Culliford AT, Krieger KH, Kloth D, Press R, Baumann FG, Spencer FC (1985) A survey of 77 major infectious complications of median sternotomy: A review of 7,949 consecutive operative procedures. Ann Thorac Surg 40:214–223.

Harbarth S, Liassine N, Dharan S, Herrault P, Auckenthaler R, Pittet D (2000) Risk factors for persistent carriage of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 31:1380–1385.

Herwaldt LA (2003) Staphylococcus aureus nasal carriage and surgical-site infections. Surgery 134:S2–S9.

Herwaldt LA, Cullen JJ, French P, Hu J, Pfaller MA, Wenzel RP, Perl TM (2004) Preoperative risk factors for nasal carriage of Staphylococcus aureus. Infect Control Hosp Epidemiol 25:481–484.

Hidron AI, Kourbatova EV, Halvosa JS, Terrell BJ, McDougal LK, Tenover FC, Blumberg HM, King MD (2005) Risk factors for colonization with methicillin-resistant Staphylococcus aureus (MRSA) in patients admitted to an urban hospital: Emergence of community-associated MRSA nasal carriage. Clin Infect Dis 41:159–166.

Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC (1997) Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 40:135–136.

Jernigan JA (2004) Is the burden of Staphylococcus aureus among patients with surgical-site infections growing? Infect Control Hosp Epidemiol 25:457–460.

Jevons MP, COE AW, Parker MT (1963) Methicillin resistance in staphylococci. Lancet 1:904–907.

Kalmeijer MD, Coertjens H, van Nieuwland-Bollen PM, Bogaers-Hofman D, de Baere GA, Stuurman A, van Belkum A, Kluytmans JA (2002) Surgical site infections in orthopedic surgery: The effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study. Clin Infect Dis 35:353–358.

Kluytmans JA, Mouton JW, VandenBergh MF, Manders MJ, Maat AP, Wagenvoort JH, Michel MF, Verbrugh HA (1996) Reduction of surgical-site infections in cardiothoracic surgery by elimination of nasal carriage of Staphylococcus aureus. Infect Control Hosp Epidemiol 17:780–785.

Kreter B, Woods M (1992) Antibiotic prophylaxis for cardiothoracic operations. Meta-analysis of thirty years of clinical trials. J Thorac Cardiovasc Surg 104:590–599.

Laupland KB, Conly JM (2003) Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: An evidence-based review. Clin Infect Dis 37:933–938.

Lin CH, Hsu RB, Chang SC, Lin FY, Chu SH (2003) Poststernotomy mediastinitis due to methicillin-resistant Staphylococcus aureus endemic in a hospital. Clin Infect Dis 37:679–684.

Maki DG, Bohn MJ, Stolz SM, Kroncke GM, Acher CW, Myerowitz PD (1992) Comparative study of cefazolin, cefamandole, and vancomycin for surgical prophylaxis in cardiac and vascular operations. A double-blind randomized trial. J Thorac Cardiovasc Surg 104:1423–1434.

Manian FA, Meyer PL, Setzer J, Senkel D (2003) Surgical site infections associated with methicillin-resistant Staphylococcus aureus: Do postoperative factors play a role? Clin Infect Dis 36:863–868.

Martone WJ (1998) Spread of vancomycin-resistant enterococci: Why did it happen in the United States? Infect Control Hosp Epidemiol 19:539–545.

McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS (2004) Surgical-site infection due to Staphylococcus aureus among elderly patients: Mortality, duration of hospitalization, and cost. Infect Control Hosp Epidemiol 25:461–467.

Mekontso-Dessap A, Kirsch M, Brun-Buisson C, Loisance D (2001) Poststernotomy mediastinitis due to Staphylococcus aureus: Comparison of methicillin-resistant and methicillin-susceptible cases. Clin Infect Dis 32:877–883.

Melzer M, Eykyn SJ, Gransden WR, Chinn S (2003) Is methicillin-resistant Staphylococcus aureus more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis 37:1453–1460.

Monnet DL, MacKenzie FM, Lopez-Lozano JM, Beyaert A, Camacho M, Wilson R, Stuart D, Gould IM (2004) Antimicrobial drug use and methicillin-resistant Staphylococcus aureus, Aberdeen, 1996–2000. Emerg Infect Dis 10:1432–1441.

Muller AA, Mauny F, Bertin M, Cornette C, Lopez-Lozano JM, Viel JF, Talon DR, Bertrand X (2003) Relationship between spread of methicillin-resistant Staphylococcus aureus and antimicrobial use in a French university hospital. Clin Infect Dis 36:971–978.

Munoz P, Menasalvas A, Bernaldo de Quiros JC, Desco M, Vallejo JL, Bouza E (1997) Postsurgical mediastinitis: A case–control study. Clin Infect Dis 25:1060–1064.

Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM (2003) SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol 24:362–386.

Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, Twombley J, French PP, Herwaldt LA (2002) Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med 346:1871–1877.

Reagan DR, Doebbeling BN, Pfaller MA, Sheetz CT, Houston AK, Hollis RJ, Wenzel RP (1991) Elimination of coincident Staphylococcus aureus nasal and hand carriage with intranasal application of mupirocin calcium ointment. Ann Intern Med 114:101–106.

Saginur R, Croteau D, Bergeron MG (2000) Comparative efficacy of teicoplanin and cefazolin for cardiac operation prophylaxis in 3027 patients. The ESPRIT Group. J Thorac Cardiovasc Surg 120:1120–1130.

Salminen US, Viljanen TU, Valtonen VV, Ikonen TE, Sahlman AE, Harjula AL (1999) Ceftriaxone versus vancomycin prophylaxis in cardiovascular surgery. J Antimicrob Chemother 44:287–290.

Scully BE, Briones F, Gu JW, Neu HC (1992) Mupirocin treatment of nasal staphylococcal colonization. Arch Intern Med 152:353–356.

Sharma M, Berriel-Cass D, Baran J Jr (2004) Sternal surgical-site infection following coronary artery bypass graft: Prevalence, microbiology, and complications during a 42-month period. Infect Control Hosp Epidemiol 25:468–471.

Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E, Jarvis WR (1999) Emergence of vancomycin resistance in Staphylococcus aureus. Glycopeptide-Intermediate Staphylococcus aureus Working Group. N Engl J Med 340:493–501.

Tacconelli E, Venkataraman L, De Girolami PC, DAgata EM (2004) Methicillin-resistant Staphylococcus aureus bacteraemia diagnosed at hospital admission: Distinguishing between community-acquired versus healthcare-associated strains. J Antimicrob Chemother 53:474–479.

The European Antimicrobial Resistance Surveillance System (2004) EARSS Annual Report 2004. Accessed at http://www.rivm.nl/earss/result/Monitoring_reports/.

Tiemersma EW, Bronzwaer SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, Monen J, Witte W, Grundman H (2004) Methicillin-resistant Staphylococcus aureus in Europe, 1999–2002. Emerg Infect Dis 10:1627–1634.

Troillet N, Carmeli Y, Samore MH, Dakos J, Eichelberger K, DeGirolami PC, Karchmer AW (1998) Carriage of methicillin-resistant Staphylococcus aureus at hospital admission. Infect Control Hosp Epidemiol 19:181–185.

Vardakas KZ, Soteriades ES, Chrysanthopoulou SA, Papagelopoulos PJ, Falagas ME (2005) Perioperative anti-infective prophylaxis with teicoplanin compared to cephalosporins in orthopaedic and vascular surgery involving prosthetic material. Clin Microbiol Infect 11:775–777.

von Eiff C, Becker K, Machka K, Stammer H, Peters G (2001) Nasal carriage as a source of Staphylococcus aureus bacteremia. N Engl J Med 344:11–16.

Vuorisalo S, Pokela R, Syrjala H (1998) Comparison of vancomycin and cefuroxime for infection prophylaxis in coronary artery bypass surgery. Infect Control Hosp Epidemiol 19:234–239.

Weber SG, Gold HS, Hooper DC, Karchmer AW, Carmeli Y (2003) Fluoroquinolones and the risk for methicillin-resistant Staphylococcus aureus in hospitalized patients. Emerg Infect Dis 9:1415–1422.

Wernitz MH, Swidsinski S, Weist K, Sohr D, Witte W, Franke KP, Roloff D, Ruden H, Veit SK (2005) Effectiveness of a hospital-wide selective screening programme for methicillin-resistant Staphylococcus aureus (MRSA) carriers at hospital admission to prevent hospital-acquired MRSA infections. Clin Microbiol Infect 11:457–465.

Wertheim HF, Vos MC, Ott A, van BA, Voss A, Kluytmans JA, van Keulen PH, Vandenbroucke-Grauls CM, Meester MH, Verbrugh HA (2004) Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet 364:703–705.

Wilson AP, Treasure T, Gruneberg RN, Sturridge MF, Ross DN (1988) Antibiotic prophylaxis in cardiac surgery: A prospective comparison of two dosage regimens of teicoplanin with a combination of flucloxacillin and tobramycin. J Antimicrob Chemother 21:213–223.

Zanetti G, Goldie SJ, Platt R (2001) Clinical consequences and cost of limiting use of vancomycin for perioperative prophylaxis: Example of coronary artery bypass surgery. Emerg Infect Dis 7:820–827.

Zanetti G, Platt R (2004) Antibiotic prophylaxis for cardiac surgery: Does the past predict the future? Clin Infect Dis 38:1364–1366.

*This page intentionally blank*

# Chapter 16
# Control of Healthcare-Associated Methicillin-Resistant *Staphylococcus aureus*

Jan A. J. W. Kluytmans and Bram M. W. Diederen

## Introduction

As long as we are able to identify the causative microorganism for infections, *Staphylococcus aureus* has been the most important cause of nosocomial infections (Archer 2000). The consequences of infections are severe, especially when there is no effective antimicrobial treatment available. In 1941 the mortality rate of *S. aureus* bacteremia at the Boston City hospital was reported to be 82% (Skinner and Keefer 1941). A recent study estimated that inpatients with *S. aureus* infections in U.S. hospitals had approximately three times the length of hospital stay, three times the total charges, and five times the risk of in-hospital death when compared to inpatients without infection (Noskin et al. 2005). Applying these data to the annual total of U.S. inpatients results in an estimated $9.5 billion additional costs and close to 12,000 inpatient deaths per year.

The history and evolution of *S. aureus* reflects the interaction between pathogenic organisms and antibiotic usage: the introduction of an effective antimicrobial with subsequent widespread usage invariably results in the eventual development of resistance and the consequent dissemination of resistance determinants. At the introduction of benzylpenicillin into chemotherapy in the early 1940s, *S. aureus* isolates were fully susceptible and several of the first successes of penicillin therapy were related to the cure of formerly untreatable staphylococcal diseases. By the mid 1950s the number of *S. aureus* clinical isolates showing high-level resistance to penicillin (due to the acquisition of a plasmid-borne penicillinase) increased rapidly, to such an extent that penicillin ceased to be a useful therapeutic agent against staphylococcal infections. Methicillin, originally called celbenin, was the first mechanism-based antimicrobial agent: it is a semisynthetic derivative of penicillin chemically modified to withstand the degradative action of penicillinase. The drug was introduced into therapy in Europe in 1959–1960. However, only 1 year later, the first methicillin-resistant *S. aureus* (MRSA) strains were detected (Jevons 1961), and the first clinical failure by an MRSA strain was described (Dowling 1961), followed by a report on the first MRSA outbreak in 1963 (Stewart and Holt 1963). Since then, MRSA has become the most prevalent pathogen causing

hospital infection throughout the world, and MRSA incidence is still increasing in many countries (Voss et al. 1994, Tiemersma et al. 2004).

Although MRSA has become a worldwide problem, the incidence of MRSA varies widely between countries. The incidence of MRSA also varies between hospitals within countries (Tiemersma et al. 2004). For instance, in Belgium the proportion of *S. aureus* isolates that were resistant to methicillin ranged from 1.6% to 62.4%, with a mean of 21.3% (Struelens et al. 1996). The incidence is consistently higher in the United States, Japan, and southern Europe than in other countries; in these countries more than 40% of *S. aureus* infections are caused by MRSA, compared with less than 2% in Scandinavia, the Netherlands, and Switzerland (Diekema et al. 2001). In the Netherlands, MRSA rates in hospitals have thus far remained negligible, probably as a result of a combination of a restrictive antibiotic policy coupled with strict and well-enforced infection control measures.

While the question of whether there is increased mortality associated with methicillin resistance remains unanswered for some, there is no doubt that HA-MRSA infections are associated with longer hospital stays and higher costs (Cosgrove et al. 2005). In addition, HA-MRSA also has a major impact on other resources such as isolation facilities and bed management. Probably the most important observation is that MRSA infections are additional to the preexisting burden of disease due to methicillin-susceptible *S. aureus* (Wenzel et al. 1991). Crowcroft et al. showed increasing mortality from MRSA in England and Wales paralleling the increase in bacteremias with MRSA (Crowcroft et al. 2003).

Treatment options for HA-MRSA infections are limited as the majority of HA-MRSA exhibit a multidrug-resistant phenotype with variable resistance to macrolides, quinolones, tetracyclines, and aminoglycosides among other antibiotics in addition to the broad-base resistance to β-lactam antibiotics. Treatment results with vancomcyin, the gold standard antibiotic against MRSA, is less than ideal in view of suboptimal efficacy, lack of an oral formulation, increased toxicity, and higher costs compared to β-lactam antibiotics. Reports of vancomycin intermediately susceptible *S. aureus* (VISA), first isolated in Japan in 1997, and vancomycin-resistant *S. aureus* (VRSA) caused widespread alarm among physicians as it was feared that we are entering an era of untreatable *S. aureus* infections. MRSA evolves to VRSA by acquiring the plasmid-borne *vanA* gene from vancomycin resistant enterococci (VRE). Both VRSA and VISA represent evolutionary steps taken by *S. aureus* to adapt to the nosocomial milieu of increased glycopeptide use.

Since the first reports the paradigm for MRSA acquisition was that it occurred exclusively in the healthcare setting; MRSA is considered a multidrug-resistant pathogen that is strongly associated with infections in individuals with established risk factors associated with healthcare facilities. Recently, however, cases of MRSA have been documented among healthy community-dwelling persons without these established risk factors for MRSA acquisition, resulting in the further classification of MRSA into whether they are healthcare- or community-associated (Boyce 1998, Deresinski 2005). Despite their designation as community-associated MRSA

strains (CA-MRSA), these strains are not restricted to that setting, since CA-MRSA strains have been found in association with nosocomial infections as well (Carleton et al. 2004). While a discussion of CA-MRSA is beyond the scope of this chapter, this phenomenon should be kept in mind as a trend that may potentially impact on several existing strategies for the control of HA-MRSA.

## Mechanism of Resistance and Molecular Background of HA-MRSA

Resistance to methicillin confers resistance to all beta-lactam antibiotics and requires the presence of the *mecA* gene, encoding the production of PBP 2a (Chambers 1997). The origin of the *mec* element is not known. The assembly of the several *mec* element structures that have been found may have evolved from multiple hosts, possibly among coagulase-negative staphylococci. PBP 2a is a transpeptidase that catalyzes the formation of cross-bridges in bacterial cell wall peptidoglycan, and has a low affinity for all β-lactam antibiotics. It takes over the function of cell wall biosynthesis in the presence of β-lactam antibiotics when normally occurring PBPs are inactivated by ligating β-lactams. The *mecA* gene is carried on a mobile genetic element known as the staphylococcal cassette chromosome (SCC) *mec*. Besides the *mecA* gene itself, the SCC*mec* element contains regulatory genes, an insertion sequence element, and a unique cassette of recombinase genes responsible for the integration and excision of SCC*mec*. At present, five types of SCC*mec* elements have been identified based on the class of *mecA* gene complex and the type of *ccr* gene complex, and are numbered from I to V (Deresinski 2005). Type I SCC*mec* contains the *mecA* gene as the sole resistance determinant, whereas SCC*mec* types II and III contain multiple determinants for resistance to non-β-lactam antibiotics and are responsible for the multidrug resistance commonly found in HA-MRSA isolates. Strains of community-acquired MRSA that have emerged over the past decade have mostly harbored the SCC*mec* type IV element and they are typically susceptible to multiple antibiotics with non-β-lactam susceptibility patterns resembling those of methicillin-susceptible *S. aureus* (MSSA) strains prevalent in the community.

Genetic evolutionary analyses have demonstrated that the *mecA* gene has been transferred into MSSA on at least 20 occasions, having emerged in five phylogenetically distinct lineages, as well as reemerging within indvidual lineages (Enright et al. 2002). This indicates that the gene for methicillin resistance has been horizontally transferred at least five times in *S. aureus*. The genetic background represented by CA-MRSA represents the sixth genetic background that is known to contain SCC*mec* DNA (Deresinski 2005). What is clear from molecular typing studies is that a small number of ecologically successful genetic backgrounds can acquire the methicillin resistance gene and retain a high level of epidemicity. The current understanding is that MRSA arose as a result of the transfer of SCC*mec* into MSSA. As a point of interest, this phenomenon seems to have occurred infrequently in the past and there are relatively few genotypes of

MRSA as opposed to MSSA, an observation that is backed by a recent study demonstrating that certain *S. aureus* lineages were more permissive of *mecA* and its gene product than others (Katayama et al. 2005). These findings suggest that virtually all patients with MRSA infection or colonization have acquired their MRSA strain from an external source, and therefore control efforts must mainly focus on preventing transmission.

## Treatment of MRSA Infections

The therapeutic approach to patients with MRSA infection depends on the site of infection and the *in vitro* susceptibility pattern of the infecting strain. The site of infection, and the removal of an infected device or drainage of an abscess, are often more important than antimicrobial therapy, as is the case for all staphylococcal infections. Superficial infections often do not require systemic antimicrobial treatment. The emergence of MRSA infections in the community also places emphasis on the importance of nonantibiotic management of localized infections. Although sometimes neglected, appropriate drainage is the optimal management of many skin and soft tissue infections. Antibiotic therapy is merely an adjunct in deeper, closed-space infections. Cutaneous abscesses typically resolve with proper drainage and/or debridement alone, and collections left without drainage in the setting of antibiotic treatment promote the emergence of resistance.

The current drug of choice for serious infections with MRSA remains vancomycin at most institutions. It is bactericidal for most Gram-positive bacteria with activity directed against the bacterial cell wall, where it inhibits the synthesis and assembly of peptidoglycan polymers by complexing with D-alanyl-D-alanine precursor. There are a number of issues concerning the use of this drug. First, vancomycin can only be given intravenously for the treatment of infections caused by MRSA. Second, treatment results are inferior compared to the use of β-lactams for *S. aureus*. Treatment failures have been reported with glycopeptides in the treatment of staphylococcal endocarditis, and its effectiveness has been questioned based on the high rate of unsatisfactory response among intravenous drug users with *S. aureus* endocarditis, the slow response in patients with MRSA endocarditis, and the higher failure rate in a 14-day course of therapy for right-sided methicillin-susceptible *S. aureus* endocarditis when vancomycin or teicoplanin were compared with cloxacillin (Murray and Nannini 2005). Third, vancomycin use is thought to be one of several factors associated with the spread of VRE, and this has possibly resulted in the development of VRSA by transfer of the *vanA* gene into MRSA.

There has been a recent expansion in the number and variety of antimicrobials available for the treatment of MRSA and other Gram-positive infections, such as linezolid, quinupristin-dalfopristin, and daptomycin. Although many of these and other new antibiotics against Gram-positive bacteria are merely derivatives of established antimicrobial classes, others have novel mechanisms of activity and appear at preliminary stages to have activity surpassing that of current glycopeptide therapeutic

standards against MRSA. These drugs considerably expand the available choice of agents against MRSA, and could significantly lessen the impact of MRSA developing glycopeptide resistance. It is likely that the current glycopeptides will be replaced by one of these newer agents as the gold standard of therapy for MRSA infections in the near future. The question is, how long will any of these agents remain efficacious before resistance becomes widespread? Given the history of *S. aureus*, the development of resistance to any new agent is merely a matter of time, and resistance to linezolid, quinupristin-dalfopristin, and daptomycin resulting in therapeutic failure has already been reported (Hancock 2005).

## The Epidemiology of MRSA

*S. aureus* is a human commensal, colonizing predominantly the anterior nares of approximately 30% of the general population, with subgroups such as insulin-dependent diabetes mellitus, or dialysis-dependent renal failure having higher carriage rates (Kluytmans et al. 1997). Risk factors for MRSA colonization and infection change over time and with the evaluated population; identified risk factors vary depending on whether patients with MRSA infection or colonization were studied and vary by geographical location and demographic characteristics of the patient population. Numerous studies have looked at risk factors for MRSA colonization and infection, both at admission and during hospitalization. Risk factors that have been described for hospital acquisition of MRSA include antimicrobial exposure, length of stay in the hospital or intensive care unit, colonization pressure, and illness severity. Risks for colonization or infection at admission have included previous hospitalization, exposure to a long-term care facility, increased age, presence of open skin lesions, and presence of a central venous catheter (Karchmer 2005).

Regardless of whether they are resistant to antibiotics, multiple reservoirs and routes of transmission exist when considering the epidemiology of *S. aureus*. The primary nosocomial reservoir for MRSA is colonized or infected patients. The nares, wounds, and rectum are the most common sites of colonization in both acute and long-term facilities. While carriers (especially those with MRSA) have a higher risk of developing infection subsequently, the majority are asymptomatic and potentially serve as reservoirs for the subsequent transmission of the organism. The critical infection control containment measure for MRSA is early recognition of the colonized patient. Infected patients are easily recognized as infected and are handled with precautions. Colonized patients are often not detected since cultures are not taken routinely in most settings. Therefore, they pose a greater threat of spreading MRSA than infected patients. Colonized or infected healthcare workers (HCWs) also serve as reservoirs of MRSA but are probably only of significant impact when they remain colonized for prolonged periods.

Most transmission of MRSA from patient to patient is thought to be mediated by transiently colonized HCWs, although airborne dispersal and transmission through contacts with contaminated surfaces may also be important (Solberg 2000).

Epidemiologic data have shown for more than a century and a half that HCWs spread microbes from patients to patient via transiently contaminated hands. Sometimes HCWs are colonized in the nose. Most likely, staphylococcal nasal carriers contaminate their fingers and hands by direct contact with the anterior nares, as suggested by Hare and Thomas (1956). A controlled trial published in 1966 showed that refraining from hand hygiene was associated with significantly greater spread of *S. aureus* (Mortimer et al. 1966). The extent to which contaminated environmental surfaces contribute to transmission of MRSA to patients has not been established. The main reason for this is that whenever there is a possibility for transfer via contaminated surfaces, there is always the possibility of transfer by other routes. However, the environment can become heavily colonized with MRSA and may serve as the reservoir for continued spread of the organism (Crossley et al. 1979). In one report, 35% of inanimate surfaces cultured from the rooms of patients with MRSA in a wound or in urine were contaminated with the organism. In comparison, only 6% of surfaces were contaminated when patients had MRSA in sites other than a wound or urine (Boyce et al. 1997). An important observation was made by Davies and Noble (1962) who demonstrated that large numbers of skin fragments were dispersed into the air during activities such as bedmaking, and that *S. aureus* could be cultivated from the epithelial fragments. Airborne transmission of MRSA can occur when nurses are changing dressings or bedding of patients who have large burns, wounds, or areas of dermatitis that are infected or heavily colonized with MRSA (Cookson et al. 1989). Also, carriers who have common colds can disperse MRSA in the surrounding air (Sheretz et al. 1996). Few guidelines have addressed the possibility of airborne transmission so far.

## Prevention and Control of Infection

Given the clinical burden and added costs associated with HA-MRSA infections, attempts should be undertaken to prevent colonization and subsequent infection. Control strategies should include screening and isolation of patients with high risk of carrying MRSA, implementation of an infection control program to prevent transmission of MRSA, and a proper antibiotic policy to minimize antibiotic pressure and resistance development.

### *Antibiotic Control*

The high prevalence of antibiotic therapy in hospitals ensures that any microbe with almost any mechanism of resistance will enjoy a selective advatage to survive, proliferate, and spread. The risk of MRSA colonization has been shown to relate to the frequency and duration of prior antimicrobial therapy (Monnet 1998). Other studies have reported on the contribution of antimicrobial drug use to MRSA colonization and infection in patients, or to high MRSA rates in healthcare settings (Hill et al. 1998, Landman et al. 1999). Using a statistical model Monnet et al. (2004) provided evidence of a temporal relationship between antimicrobial

drug use and the varying prevalence of MRSA over time during an outbreak in a single hospital in Aberdeen, Scotland. Only three classes of antimicrobial drugs, namely, third-generation cephalosporins, fluoroquinolones, and macrolides, showed this relationship. Various mathematical models have appeared in the literature addressing different aspects of multiresistant pathogens, and predicted that the effect of antimicrobial prescribing patterns in an outbreak situation is likely to be slight (Bonten et al 2001, Sebille et al. 1997). While antibiotics give MRSA a selective advantage over its susceptible counterpart, strict policies to limit the use of antibiotics are usually not enough to reverse its spread; control of MRSA depends principally on sustained efforts to prevent transmission.

## *Infection Control*

### Basic Infection Control Measures

In 1996, the Hospital Infection Control Practices Advisory Committee (HICPAC) recommended a number of isolation and barrier precaution practices for HCWs when caring for patients with MRSA (Garner 1996). The most fundamental measure to reduce cross-infection is hand hygiene. It is amazing how low compliance to this important and simple measure is. However, hand hygiene alone is not enough to control MRSA. The Centers for Disease Control and Prevention (CDC) published a guideline in 2002, recommending a number of new strategies for improving hand hygiene among HCWs (Boyce and Pittet 2002). The Society for Healthcare Epidemiology of America (SHEA) published a further reaching guideline in 2003 to prevent transmission of multidrug-resistant strains of *S. aureus* and enterococci (Muto et al. 2003). Most basic infection control meausures are widely agreed upon, including identification and isolation of patients infected or colonized with MRSA in a single room with toilet and hand-washing facilities, hand disinfection between patients, wearing of gloves and gowns, and a high standard of aseptic techniques and ward cleaning. When it comes to wearing of face masks, recommendations vary. Some feel that masks are rarely necessary, except perhaps for procedures that may generate staphylococcal aerosols, such as sputum suction and chest physiotherapy, or patients with exfoliative skin conditions (Mulligan et al. 1993). Others, such as the Dutch Infection Prevention Working Party, recommend the use of masks when entering the room of a colonized individual. The importance of airborne transmission has been demonstrated in early studies where *S. aureus* carriers and noncarriers among bedridden patients in the same room have been treated by separate teams of nurses to eliminate transmission by contact (Mortimer et al. 1966). Probably not all carriers will shed MRSA into their environment, but this may easily change with the onset of, for example, a viral respiratory infection or in patients with symptomatic allergic rhinitis (Sheretz et al. 1996, Bassetti et al. 2003). Maybe even more important than the prevention of airborne infection is the wearing of masks to prevent touching of the face during the stay in the room. This is done

frequently and unconsciously by most individuals. Therefore, wearing of face masks is an important measure to prevent transmission of MRSA.

Control of MRSA in healthcare facilities demands a strict adherence to infection control practices, and education of hospital personnel is an essential part of any infection control program. The education should include all hospital staff associated with patient care, including physicians, nurses, technicians, housekeeping, and medical administration. Effective infection control can only be achieved when all personnel are motivated to follow the rules given by an expert on infection control practices. Improved knowledge about the best ways to ensure favorable infection control practices is highly appreciated. This is particularly true for compliance with such an important but simple measure of hand disinfection (Albert 1981). Undoubtedly, an effective infection control team is essential for compliance with prescribed hospital infection control practices.

### Role of the Microbiology Laboratory

Basic infection control is mandatory for an effective control of MRSA but by itself insufficient to guarantee low rates of MRSA. Clinical microbiology laboratories provide several services that are important in controlling transmission of MRSA in healthcare facilities. The SHEA guidelines recommend the use of active surveillance cultures to screen patients at high risk for MRSA colonization (Muto et al. 2003). The optimal culture methods are still subject to debate. It is unclear which sites should be sampled. Most guidelines agree on sampling of the nose and wounds. However, a significant percentage of colonized individuals carry only in the throat or perineal area (van Griethuysen et al. 2003). Also the methods applied in the laboratory vary. This variation concerns both the kind of agar to be used, and the use of a broth enrichment medium. Several investigators have shown that the use of a broth enrichment medium increases the yield of MRSA significantly. Van Ogtrop found that without broth enrichment, 44.6% of all cultures yielding MRSA would have been missed (van Ogtrop 1995). In another study the addition of a broth enrichment medium detected between 19.1 and 32.0% more MRSA-positive specimens and between 13.3 and 23.3% more MRSA-positive patients per surveillance event (Gardam et al. 2001). Finally, the correct identification of *S. aureus* and detection of methicillin resistance is of great importance and may be difficult. Newly identified patients or HCWs should be confirmed by molecular methods.

To control MRSA more effectively, rapid and accurate screening tests for MRSA are needed to identify patients who are candidates for contact precautions. However, standard MRSA culture methods take at least 48 h to perform, with the possible consequences that patients might needlessly be placed under contact precautions for days, or that MRSA transmission risk might increase if patients are placed under contact precautions only after MRSA culture results become available. Rapid tests would decrease delays in implementing contact precautions for MRSA-colonized patients and, theoretically, would further decrease the risk for nosocomial transmission. A sensitive and specific real-time PCR assay for

MRSA is now available that identifies MRSA from a nasal swab in less than 1 h (Huletsky et al. 2005). The results of MRSA PCR were compared to those obtained using primary plating on a mannitol-salt agar medium. Further studies are needed to evaluate the promising role of PCR technology for rapid and accurate detection of MRSA in surveillance specimens. Although not as rapid as molecular-based assays, culture methods using selective chromogenic agar may also decrease MRSA detection time by 1–2 days, compared with the time associated with standard culture (Diederen et al. 2005).

When clusters or outbreaks of MRSA occur in hospitals, it is important to determine if the phenomenon represents nosocomial transmission of a single strain, or clusters of cases caused by multiple unrelated strains. For most hospitals, analysis of antibiotic susceptibility patterns (antibiograms) of isolates represents the most practical initial approach to typing. However, genotypic methods have superior discriminatory power and should be used whenever possible. Although multiple molecular methods exist for the typing of *S. aureus*, it is widely acknowledged that the reference standard for the typing of strains within an institution is pulsed-field gel electrophoresis (PFGE), whereas multilocus sequence typing (MLST) is the reference standard for assessing phylogenetic relationships between isolates (Chambers 1997). In recent years, an alternative PCR method comparing variable number tandem-repeats at multiple loci has been described for typing MRSA. This technique demonstrates equivalent discriminatory power compared to PFGE while being less labor- and time-intensive (Malachowa et al. 2005), and may well replace PFGE as the typing method of choice for analysis of local MRSA outbreaks and surveillance data in the future.

### Screening and Isolation

Prompt isolation of patients with MRSA is a key element in the control. Multiple studies, involving both epidemic and endemic settings, have shown that implementation of surveillance cultures to identify colonized patients and use of contact precautions have been followed by a significant reduction in the rates of both colonization and infection of patients with MRSA (Muto et al. 2003). Isolation measures for patients are intended to interrupt transmission. The most intensive forms of isolating patients are isolation rooms (designated for the treatment of known or suspected carriers of MRSA) and nurse cohorting (the physical segregation of MRSA patients in one part of a ward, with nursing by designated staff who care exclusively for these patients). Other isolation measures include the use of single bedded rooms, cohorts of patients on general wards (without designated nursing staff), and barrier precautions (use of aprons or gowns, gloves, and, in some cases, masks by HCWs as the only physical barrier to transmission). Such control measures may place substantial burdens on hospital resources, and the value of their continued use has been questioned. No well designed studies exist that allow the role of isolation measures alone to be assessed. Nonetheless, there is substantial evidence that concerted efforts that include isolation can reduce MRSA even in endemic settings (Cooper 2004). For instance, a study by Vriens et al. (2002) showed a 38-fold higher frequency of transmission of MRSA from

unidentified, unisolated patients as compared with identified, isolated patients in a Dutch ICU using gowns gloves and masks.

Despite controversy among infection-control practitioners about the value of specific control measures, many recent studies have shown that the spread of MRSA can be controlled by implementing preventive measures not only in hospitals in which the prevalence of MRSA is low but also in those where MRSA is highly endemic. Infection control programs that have not taken into account the role of asymptomatic carriage in the transmission of MRSA have rarely succeeded in the control of MRSA. Less stringent and more permissive programs, such as those espoused by the Healthcare Infection Control Practices Advisory Committee, have thus far failed to significantly reduce MRSA rates over the years (Diekema et al. 2001). To decrease the incidence of healthcare-associated MRSA infections, the Society for Healthcare Epidemiology of America (SHEA) has recently recommended more aggressive strategies that include active surveillance cultures for patients at high risk for MRSA colonization or infection, together with contact precautions. Although this guideline is more extensive than the previous guidelines in the United States, it is far less stringent than Scandinavian and Dutch policies. The most important difference is that the possibility of HCWs carrying and transmitting MRSA is ignored. In the Netherlands an active search strategy is followed; using this strategy it was found that more than 20% of all individuals who are colonized with MRSA are HCWs (Beaujean et al. 2005). It is questionable if a strategy that does not take this reservoir into account can be successful. The costs of maintaining a strict infection control program in a low prevalence setting, such as the Dutch "search and destroy" policy, are outweighed by the potential costs of dealing with endemic MRSA (Verhoef et al. 1999). However, to impose the "search and destroy" policy without adaptation onto institutions where the endemic MRSA rates are high is probably not cost-effective. Most likely a two-step approach is the preferred strategy. At the first step the MRSA rates should be reduced by taking less stringent control measures. When the rates have come down, the second step would be a "search and destroy" strategy to get back to a level below 1%. It is clear that the approach to control MRSA in the healthcare setting differs between hospitals where MRSA is nonendemic or endemic.

### Approach in Hospitals Where MRSA Is Not Endemic

In low prevalence settings a national "search and destroy" policy prevents MRSA from becoming endemic. Strict isolation of patients who are MRSA carriers is one of the cornerstones of this strategy and it has been practiced for several decades in Dutch and Scandinavian hospitals. Its effectiveness is measured by the low prevalence, despite frequent admissions of patients from hospitals abroad carrying MRSA. This policy works most effectively if MRSA carriage can be largely related to patients with known risk factors, such as hospitalization in foreign hospitals with a high prevalence of MRSA. In the general population of the Netherlands, the prevalence of carriage is still very low. A recent survey showed that at admission to the hospital the MRSA prevalence is 0.03% (Wertheim et al. 2004).

Patients transferred from foreign hospitals to hospitals in the Netherlands carry MRSA more than 150 times more often (Kaiser et al. 2004).

Patients at high risk for MRSA are kept in strict isolation until the results of screening cultures, taken from the nose, throat, perineum, and skin lesions, indicate that there is no colonization with MRSA. If colonization or infection with MRSA is detected, the patient will remain in isolation. Sometimes MRSA is found in a patient who was not suspected of carriage before. Then the contacts (roommates and HCWs) of this patient are screened and the roommates are isolated until results of screening are available. If transmission occurs measures are taken to contain the outbreak. Sometimes wards have to be closed for new admissions temporarily. Although the measures of a search and destroy policy are effective in maintaining a low level of MRSA, they can be costly and have a significant impact on the normal process in the hospital when larger outbreaks occur.

### Approach in Hospitals Where MRSA Is Endemic

It is possible to control MRSA even in situations of high endemicity. Denmark managed within a decade to bring down its prevalence of MRSA from more than 30% of all blood isolates of *S. aureus* in the 1960s to 1% following the institution of an infection control program. While it is difficult to assign a specific value to each component of Denmark's infection control program, it is suggestive that this and several other successful programs have incorporated the use of surveillance cultures to detect asymptomatic MRSA carriers. In areas where the MRSA prevalence is very high or resources are limited, adaptations to the above "search and destroy" policy will have to be made, but the underlying premise should be kept. A risk assessment should be performed and resources utilized in areas where the impact of MRSA transmission is most pronounced, such as the intensive-care and burns unit. Admission screening of patients entering a low-risk hospital area, such as a nonneonatal pediatric ward, should include those who are known to have been previously infected or colonized with MRSA or who are admitted from MRSA-affected hospitals, nursing homes, or hospitals abroad. These patients should, if possible, be admitted to an isolation room or ward deemed to be free of MRSA. In high-risk areas action also includes admission screening of all patients entering and all patients transferred. Screening of all patients (nose, throat, perineum, skin lesions, and manipulated sites) and staff in a unit is carried out when a single case of MRSA is encountered, and MRSA carriers are then isolated. Closure of wards is carried out only after a careful risk assessment, including various factors such as the number of MRSA cases, availability of alternative facilities locally, virulence and transmissibility of the MRSA strain, staffing levels, and whether the risk of transmission outweighs the benefit of admission.

### Eradication of MRSA Carriage

Eradication or suppression of MRSA carriage has occasionally been employed as part of infection control measures, or as a way of preventing infections in susceptible populations. The latter strategy is based on the understanding that colonization

precedes infection in the majority of *S. aureus* infections. Decolonization is most commonly attempted with at least 5 days of topical mupirocin ointment applied intranasally alone or in combination with a variety of antiseptic lotions and/or systemic oral antibiotics (such as rifampicin) to enhance the clearance of carriage from nonnasal sites (Boyce 2001). Although initial decolonization tended to be successful in nasal carriers, with up to 99% eradication, recolonization rates were high, and the efficacy of current regimens is doubtful in eradicating multiple-site carriage of MRSA (Harbarth et al. 1999). A Cochrane database review failed to find sufficient evidence for the use of current available antimicrobials in eradicating MRSA colonization (Loeb et al. 2003). What to do about decolonization? In regions with low or no MRSA endemicity, decolonization of both healthcare staff and patients is a useful adjunct measure for controlling outbreaks. Any program of decolonization therapy should incorporate susceptibility testing, as selection of inactive agents is less likely to achieve eradication. In regions with high endemicity, however, decolonization alone without ancillary infection control efforts to reduce MRSA transmission would probably result in MRSA recolonization as well as an eventual increase in mupirocin resistance rates. At present it is not clear what strategy is optimal in high endemic settings.

### Vaccination

A vaccine directed against *S. aureus* capsular polysaccharide has shown short-term efficacy in hemodialysis patients (Shinefield et al. 2002). StaphVax is a bivalent polysaccharide vaccine pending license in late 2005, targeted against *S. aureus* capsular types 5 and 8, conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A, which account for approximately 90% of all clinical isolates. A double-blind trial involving patients with end-stage renal disease who were receiving hemodialysis was performed. Efficacy was estimated by comparing the incidence of *S. aureus* bacteremia in the patients who received the vaccine with the incidence in the control patients and demonstrated 57% efficacy, with partial immunity lasting approximately 40 weeks. The authors state that because patients receiving hemodialysis are among the least likely to have a response to immunoprophylaxis, the efficacy of the vaccine might perhaps be greater in other patient populations. A potential application in the future where the vaccine's short period of immunogenicity might not pose a major problem would be immunization prior to elective surgery, especially orthopedic or cardiothoracic operations.

## Conclusion and Recommendation

HA-MRSA is a major nosocomial pathogen with major impact on the healthcare systems of almost every country in the world. In countries with high rates of HA-MRSA, mortality and morbidity attributed to infections caused by this organism is high, as is the financial burden of therapy and prolonged hospitalization. In countries with low rates, the prevention of MRSA from becoming endemic

is responsible for a lower, but still significant financial outlay. However, prevention is less expensive than therapy of MRSA infections, and intensive infection control aimed at reducing MRSA rates is strongly recommended in low-prevalence settings.

Unfortunately, in most countries MRSA has become endemic. It is not clear how to reduce MRSA rates most effectively in these settings. Screening for asymptomatic carriage, screening of HCWs, and reliable laboratory methods are crucial for success. Infection control programs that do not take into account the role of asymptomatic carriers (both patients and HCWs) have limited chances of success, at be. Two recent trends of MRSA stand out at this time: the dissemination of methicillin resistance to the community and the acquisition of vancomycin resistance determinants from VRE.

It is expected that CA-MRSA rates will further increase worldwide in the next few years. The challenge of controlling CA-MRSA in open communities is difficult even in countries with traditionally good control of HA-MRSA. Some authors predict that MRSA will become the prevalent *S. aureus* in the near future, similar to the emergence of penicillin resistance in *S. aureus* in the 1950s and 1960s (Deresinski 2005). A new paradigm of infection control is required if there is to be any hope of preventing methicillin resistance from becoming as widespread as penicillin resistance in *S. aureus*.

Recently several independent cases infected with VRSA have been reported in the United States. MRSA evolves to VRSA by acquiring the plasmid-borne *vanA* gene from VRE. This evolutionary process results in a strain which is not manageable with antimicrobial therapy and theoretically would throw us back to the preantibiotic era. To control this emerging problem the successful MRSA infection control programs employed in the Netherlands and Scandinavian countries using "search and destroy" should be implemented. The current VRSA recommendations of the Centers for Disease Control and Prevention do not include all measures of these strategies. This contains important risks for VRSA to become endemic as well.

## *References*

Albert RK, Condie F (1981) Handwashing patterns in medical intensive-care units. N Engl J Med 304:1465–1466.

Anonymous (1995) Recommendations for preventing the spread of vancomycin resistance: Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). Am J Infect Control 23:87–94.

Archer GL (2000) *Staphylococcus aureus*: A well-armed pathogen. Clin Infect Dis 26:1179–1181.

Archer GL, Niemeyer DM (1994) Original evolution of DNA associated with resistance to methicillin in staphylococci. Trends Microbiol 2:343–347.

Bassetti S, Sherertz RJ, Pfaller MA (2003) Airborne dispersal of Staphylococcus aureus associated with symptomatic rhinitis allergica. Ann Intern Med 139:W–W60.

Beaujean DJMA, Tiemersma EW, de Neeling AJ, Wannet WJB (2005) Nationale MRSA-surveillance nieuwe stijl: de resultaten na een half jaar. Infectieziektenbulletin 16: 113–116.

Bonten MJ, Austin DJ, Lipsitch M (2001) Understanding the spread of antibiotic resistant pathogens in hospitals: Mathematical models as tools for control. Clin Infect Dis 33:1739–1746.

Boyce JM (1998) Are the epidemiology and microbiology of methicillin-resistant *Staphylococcus aureus* changing? JAMA 279:623–624.

Boyce JM (2001) MRSA patients: Proven methods to treat colonization and infection. J Hosp Infect 48 Suppl A:S9–14.

Boyce JM, Pittet D (2002) Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. MMWR Recomm Rep 12 Suppl:S3–40.

Boyce JM, Potter-Bynoe G, Chenevert C, King T (1997) Environmental contamination due to methicillin-resistant *Staphylococcus aureus*: Possible infection control implications. Infect Control Hosp Epidemiol 18:622–627.

Carleton HA, Diep BA, Charlebois ED, Sensabaugh GF, Perdreau-Remington F (2004) Community-adapted methicillin-resistant *Staphylococcus aureus* (MRSA): Population dynamics of an expanding community reservoir of MRSA. J Infect Dis 190:1730–1738.

Chambers HF (1997) Methicillin resistance in staphylococci: Molecular and biochemical basis and clinical implications. Clin Microbiol Rev 10:781–791.

Cooper BS Medley GF, Stone SP, kibbler CC, Coolkson BD, Roberts JA, Duckworth G, Lai R, Ebrahim S (2004) Methcillin-resistant Staphylococcus aureus in hospitals and the community: stealth dnamics and control catastrophes. Proc Natl Acad Sci USA 101:10223–10228.

Cookson B, Peters B, Webster M, Phillips I, Rahman M, Noble W (1989) Staff carriage of epidemic methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 27:141–146.

Cosgrove SE, Qi Y, Kaye KS, Harbath S, Karchmer AW, Carmeli Y (2005) The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: Mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 26:166–174.

Crossley K, Landesman B, Zaske D (1979). An outbreak of infections caused by strains of *Staphylococcus aureus* resistant to methicillin and aminoglycosides. II. Epidemiologic studies. J Infect Dis 139:280–287.

Crowcroft NS, Lamagni TL, Rooney C, Catchpole M, Duckworth G (2003) Mortality from methicillin resistant *Staphylococcus aureus* in England and Wales [electronic response to Howard et al. Mortality from methicillin resistant *Staphylococcus aureus*, bmj.com/cgi/eletters/326/7387/501/a#30165].

Davies RR, Noble WC (1963) Dispersal of staphylococci on desquamated skin. Lancet 324:1111.

Deresinski S (2005) Methicillin-resistant *Staphylococcus aureus*: An evolutionary, epidemiologic, and therapeutic odyssey. Clin Infect Dis 40:562–573.

Diederen B, van Duijn I, van Belkum A, Willemse P, van Keulen P, Kluytmans J (2005) Performance of CHROMagar MRSA medium for detection of methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 43:1925–1927.

Diekema DJ, Pfaller MA, Schmitz FJ, Smayevsky J, Bell J, Jones RN, Beach M; SENTRY Partcipants Group (2001) Survey of infections due to *Staphylococcus* species: Frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin Infect Dis 32: S114–S132.

Dowling HF (1961) The new penicillins. Clin Pharmacol Ther 2:572–580.

Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG (2002) The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). Proc Natl Acad Sci USA 99:768–792.

Gardam M, Brunton J, Willey B, McGeer A, Low D, Conly J (2001) A blinded comparison of three laboratory protocols for the identification of patients colonized with methicillin-resistant *Staphylococcus aureus*. Infect Control Hosp Epidemiol 22:152–156.

Garner JS (1996) Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. Infect Control Hosp Epidemiol 17:53–80.

Hancock RE (2005) Mechanisms of action of newer antibiotics for Gram-positive pathogens. Lancet Infect Dis 5:209–218.

Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D (1999) Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 43:1412–1416.

Hare R, Thomas CG (1956) The transmission of *Staphylococcus aureus*. Br Med J 12:840–844.

Hill DA, Herford T, Parratt D (1998) Antibiotic usage and methicillin-resistant *Staphylococcus aureus*: An analysis of causality. J Antimicrob Chemother 42:676–677.

Huletsky A, Lebel P, Picard FJ, Bernier M, Gagnon M, Boucher N, MG (2005) Identification of methicillin resistant Staphylococcus aureus carriage in less than 1 hour during a hospital surveillance program. Clin Infect Dis 40:976–81

Jevons MP (1961) "Celbenin"-resistant staphylococci. Br Med J 1:124–125.

Kaiser AM, Schultsz C, Kruithof GJ, Debets-Ossenkop Y, Vandenbroucke-Grauls C (2004) Carriage of resistant microorganisms in repatriates from foreign hospitals to the Netherlands. Clin Microbiol Infect 10:972–979.

Karchmer TB (2005) Prevention of health care-associated methicillin-resistant *Staphylococcus aureus* infections: Adapting to a changing epidemiology. Clin Infect Dis 41:167–169.

Katayama Y, Robinson DA, Enright MC, Chambers HF (2005) Genetic background affects stability of *mecA* in *Staphylococcus aureus*. J Clin Microbiol 43:2380–2383.

Kluytmans J, van Belkum A, Verbrugh H (1997) Nasal carriage of *Staphylococcus aureus*: Epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev 10:505–520.

Landman D, Chockalingam M, Quale JM (1999) Reduction in the incidence of methicillin-resistant Staphylococcus aureus and ceftazidime-resistant *Klebsiella pneumoniae* following changes in a hospital antibiotic formulary. Clin Infect Dis 28:1062–1066.

Loeb M, Main C, Walker-Dilks C, Eady A (2003) Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. Cochrane Database Syst Rev 4:CD003340.

Malachowa N, Sabat A, Gniadkowski M, Krzyszton-Russjan J, Empel J, Miedzobrodzki J, Kosowska-Shick K, Appelbaum PC, Hryniewicz W (2005) Comparison of multiple-locus variable-number tandem-repeat analysis with pulsed-field gel electrophoresis, *spa* typing, and multilocus sequence typing for clonal characterization of *Staphylococcus aureus* isolates. J Clin Microbiol. 43:3095–3100.

Monnet DL (1998) Methicillin-resistant *Staphylococcus aureus* and its relationship to antimicrobial use: Possible implications for control. Infect Control Hosp Epidemiol 19:552–559.

Monnet DL, MacKenzie FM, López-Lozano JM, Arielle Beyaert A, Camacho M, Wilson R, Stuart D, Gould IM (2004) Antimicrobial drug use and methicillin-resistant *Staphylococcus aureus*, Aberdeen, 1996–2000. Emerg Infect Dis 10:1432–1441.

Mortimer EA, Wolinsky E, Gonzaga AJ, Rammelkamp CH (1966) Role of airborne transmission in staphylococcal infections. Br Med J 1:319–322.

Mulligan ME, Murray-Leisure KA, Ribner BS, Sandiford HC, John JF, Korvick JA, kauffman CA, Yu VL (1993) Methicillin resistant Staphylococcus aureus: a consesus review of the microbiology, pathogensis, and epidemiology with implications for prevention and management. Am J Med 94:313–323

Murray BE, Nannini EC (2005) Glycopeptides (vancomycin and teicoplanin), streptogramins (quinupristin-dalfopristin), and lipopeptides (daptomycin), in Mandell GL, Bennett JE, Dolin R (eds). Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, ed 6. Philadelphia, Churchill Livingstone, pp 417–434.

Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, et al (2003) SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. Infect Control Hosp Epidemiol 24:362–336.

Noskin GA, Rubin RJ, Schentag JJ, Kluytmans J, Hedblom EC, Smulders M, Lapetina E, Gemmen E (2005)The burden of *Staphylococcus aureus* infections on hospitals in the United States: An analysis of the 2000 and 2001 nationwide inpatient sample database. Arch Intern Med 165:1756–1761.

Sebille V, Chevret S, Valleron AJ (1997) Modelling the spread of resistant nosocomial pathogens in an intensive care unit. Infect Control Hosp Epidemiol 18:84–92.

Sheretz RJ, Reagan DR, Hampton KD, Robertson KL, Streed SA, Hoen HM, Thomas R, Gwaltney JM (1996) Cloud adult: The *Staphylococcus aureus*–virus interaction revisited. Ann Intern Med 124:539–547.

Shinefield H, Black S, Fattom A, Horwith G (2002) Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. N Engl J Med 346:491–496.

Skinner D, Keefer CS (1941) Significance of bacteremia caused by *Staphylococcus aureus*. Arch Intern Med 68:851–875.

Solberg CO (2000) Spread of *Staphylococcus aureus* in hospitals: Causes and prevention. Scand J Infect Dis 32:587–595.

Stewart GT, Holt RJ (1963) Evolution of natural resistance to the newer penicillin. Br Med J 1:308–311.

Stone PW, Larson E, Kawar LN (2002) A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990–2000. Am J Infect Control 30:145–152.

Struelens J, Ronveaux O, Jans B, Mertens R (1996) Methicillin-resistant *Staphylococcus aureus* epidemiology and control in Belgian hospitals, 1991 to 1995. Groupement pour le Depistage, l'Etude et la Prevention des Infections Hospitalieres. Infect Control Hosp Epidemiol 17:503–508.

Tiemersma EW, Bronzwar SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, Monen J, Witte W, Grundman H; European Antimicrobial Resistance Surveillance System Participants (2004) Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. Emerg Infect Dis 10:1627–1634.

van Griethuysen A, de Neeling H, Vandenbroucke-Grauls C, Vos G, Kluytmans J (2003) Richtlijn detectie van meticillineresistente *Staphylococcus aureus* in Nederland. Ned Tijdschr Med Microbiol 11:58–65.

van Ogtrop ML (1995) Effect of broth enrichment cultures on ability to detect carriage of *Staphylococcus aureus*. Antimicrob Agents Chemother 39:2169.

Verhoef J, Beaujean D, Blok H, Baars A, Meyler A, van der Werken C, Weersink A (1999) A Dutch approach to methicillin-resistant *Staphylococcus aureus*. Eur J Clin Microbiol Infect Dis 18:461–466.

Voss A, Milatovic D, Wallrauch-Schwarz C, Rosdahl VT, Braveny I (1994) Methicillin-resistant *Staphylococcus aureus* in Europe. Eur J Clin Microbiol Infect Dis 13:50–55.

Vriens MR, Fluit AC, Troelstra A, Verhoef J, van der Werken C (2002) Is methicillin-resistant *Staphylococcus aureus* more contagious than methicillin-susceptible *S. aureus* in a surgical intensive care unit? Infect Control Hosp Epidemiol 23:491–494.

Wenzel RP, Nettleman MD, Jones RN, Pfaller MA (1991) Methicillin-resistant *Staphylococcus aureus*: Implications for the 1990s and effective control measures. Am J Med 91(3B):221S–227S.

Wertheim HF, Vos MC, Boelens HA, Voss A, Vandenbroucke-Grauls CM, Meester MH, Kluytmans JA, van Keuten PH,Verbrugh HA. Low prevalence of methicillin-resistant Staphylococcus aureus (MRSA) at hospital admission in the Netherlands: the value of search and destroy and restrictive antibiotic use. J Hosp Infect. 2004 Apr;56(4)321–5.

*This page intentionally blank*

# Index