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CURRENT TOPIC: INTRODUCTION

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The management of infections due to drug-resistant gram-positive bacteria

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Antimicrobial resistance is an unwelcome companion of the successful clinical deployment of antimicrobial agents during the past 70 years. Despite sometimes heroic efforts to identify and deal with this problem, resistant organisms and the clinical problems associated with them continue to multiply throughout the world. Among bacteria, resistance to antimicrobial agents is seen in all species. In recent years, however, some of the most dramatic increases and problems associated with resistance have come from methicillin-resistant *Staphylococcus aureus* (MRSA), multiply resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci (VRE). These organisms, which are fully virulent (and in some cases appear to be associated with even higher mortality rates than their more susceptible brethren), represent a major challenge for the clinician. Their continued spread and dissemination has not been effectively stopped by our best efforts at infection control, although, as will be seen in the papers in this Current Topic, we now have a much better understanding of methods that can be used to interdict their spread, at least in the hospital setting. Problems with these organisms have arisen, in large part, from our inability to control the inappropriate use of antimicrobial agents, and this represents a major challenge in curtailing further evolution and spread of antimicrobial resistance. The papers in this Current Topic review a number of the important aspects of the dissemination and clinical impact of multiply resistant gram-positive bacteria.

The problem of multiply resistant pneumococci is addressed in the paper by Fuller et al. [1]. They note that although there has been an alarming increase in the incidence of infections caused by pneumococci resistant to penicillins, macrolides, and, more recently, fluoroquinolones, these agents are still used as first-line empiric therapy in the outpatient setting. There are numerous reasons for this, including the diagnostic uncertainty that often accompanies the therapy of outpatient respiratory tract infections. In addition, there has, until recently, been a failure of studies to demonstrate the clinical relevance of resistance. Moreover, clinicians often fail to recognize clinical treatment failures. The information provided in Fuller et al.'s excellent review of pneumococci provides clear-cut data on the clinical significance of resistance to beta-lactam agents, macrolides, and fluoroquinolones, with a more than adequate demonstration of the clinical failures that can result from discordant therapy with any of these agents. They also provide valuable information to enable the clinician to quantify the risk of infection due to resistant pneumococci so that therapy can be appropriately tailored.

Penicillin-resistant *S. aureus* represents perhaps an even greater challenge. These organisms are fully virulent; indeed, infections with these organisms are likely associated with increased mortality [2]. Methicillin-resistant staphylococci are a worldwide problem, but there are some striking differences in the frequency with which they cause nosocomial infections. For instance, intensive infection control measures appear to be responsible for the low prevalence of infections with these organisms in northern Europe. This has not, however, allowed for effective control of methicillin-resistant staphylococci in the USA, southern Europe, or much of Asia. A striking exception to the "northern Europe rule" is the UK. The reasons for this are beautifully outlined in the article by I.M. Gould [3]. He notes that failures to control MRSA in the UK are presently causing a "huge public and political concern". He then provides a detailed explanation for the apparent failure to control this epidemic in the UK—an explanation that should serve as a lesson to all parts of the world where nosocomial infections with MRSA continue to be a major plague. Gould goes on to point out that the control of this organism in settings where its prevalence has been allowed to increase will require a multifaceted approach, with considerable monetary expenditure for improvement of

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infrastructure and healthcare facilities, improvement in methods of rapid detection and isolation of patients, and education in the appropriate use of antimicrobial agents, among other things.

In the intensive care unit, methicillin-resistant staphylococci are now a major cause of ventilator-associated pneumonia. M.H. Kollef reviews the antibiotic management of ventilator-associated pneumonia due to MRSA and other multiply resistant organisms [4]. He also reviews the prevalence of pneumonia due to *S. pneumoniae*, describes the epidemiology of ventilator-associated pneumonia, and provides an overview of therapeutic options for this important disease. He points out the importance of MRSA as well as resistant gram-negative organisms such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Enterobacter* species in late-onset ventilator-associated pneumonia. He goes on to define risk factors for MRSA infections in this setting and notes that MRSA is associated with a distinctly higher mortality rate than infections with MSSA in these patients. Kollef notes that antimicrobial selection for treatment of ventilator-associated pneumonia may be difficult because infection may appear to be polymicrobial and is often caused by multiresistant organisms. With respect to MRSA, Kollef points out a number of limitations of currently available therapies and provides data on alternative therapies including teicoplanin, linezolid, and clindamycin. Finally, he makes the important observation that, in appropriately selected patients, relatively short courses of therapy may be not only effective but also less likely to select resistant organisms than longer courses of treatment.

The development of resistance to vancomycin by enterococci is, without doubt, one of the more remarkable bacterial achievements because of the complexity of the genetic elements necessary for such resistance. VRE have become a major problem in the U.S. and other parts of the world. Infection with these organisms is almost invariably preceded by gastrointestinal colonization, and in recent years we have made major advances in understanding the dynamics of gastrointestinal colonization with VRE. L.B. Rice provides an insightful overview of this phenomenon [5]. He discusses a number of important studies in humans and animals which document the fact that the antimicrobial agents most likely to enhance gastrointestinal colonization with VRE include the broad-spectrum cephalosporins (with the possible exception of cefepime) and a variety of agents with activity against the gastrointestinal anaerobic flora. Moreover, in experimental animals it has been clearly shown that if the level of colonization is relatively low, certain antimicrobial agents such as piperacillin/tazobactam (which are secreted in the bile) can achieve concentrations high enough to decrease gastrointestinal colonization despite their activity against bowel anaerobes. It appears that the reason for the enhanced activity against VRE colonization is related to the ability of such agents to inhibit anaerobic organisms, which compete with enterococci for ecological niches in the gastrointestinal tract.

One of the remarkable aspects of the worldwide VRE epidemic has centered around the fact that infections with VRE have rapidly spread and become major problems among hospitalized patients in the USA but have been relatively rare in Europe, even though avoparcin was widely used as a growth promotant throughout much of Europe until the mid-1990s, when it was banned in all countries in the EU. It has been postulated that the emergence of VRE in the gastrointestinal tracts of animals treated with avoparcin resulted in organisms that lacked the virulence factors to enable them to create persistent colonization and infection in humans. In the USA, on the other hand, avoparcin was not used and there has never been a reservoir of VRE in farm animals. Thus, vancomycin resistance emerged among human isolates from the beginning and was aided and abetted by the widespread use of vancomycin and other broad-spectrum antimicrobial agents. The recent emergence of vancomycin resistance in Germany provides an opportunity to study some of the factors that are potentially associated with colonization persistence and virulence among VRE. The paper by Klare et al. [6] provides fascinating data on the spread of *Enterococcus faecium* clones exhibiting the virulence factors enterococcal surface protein (*esp*) and bacteriocin activity and, in some cases, hyaluronidase (*hyl*). By using multilocus sequence typing, the authors were able to demonstrate clonal spread of these organisms in German hospitals. An even more disturbing observation is that, in addition to their resistance to glycopeptides, some of these organisms are now also resistant to linezolid.

Because of the continued evolution of antimicrobial resistance, new antimicrobial agents active against these organisms are desperately needed. In the final paper of this Current Topic, G.M. Eliopoulos defines currently available therapeutic options for multiply resistant gram-positive bacteria [7]. He notes that certain older agents such as clindamycin and trimethoprim–sulfamethoxazole are currently being used to treat infections due to community-acquired MRSA, although clinical trials demonstrating their efficacy are lacking. The glycopeptides (vancomycin and teicoplanin) remain the standard for therapy of MRSA infections but, of course, have limited or no activity against VRE. Alternative agents for these resistant organisms that are currently approved by regulatory agencies in various parts of the world include quinupristin–dalfopristin, linezolid, daptomycin, and tigecycline. The potential utility of these drugs is described, and in conclusion, Eliopoulos discusses briefly three newer glycopeptide derivatives that are under clinical development: oritavancin, dalbavancin, and telavancin. He closes with a brief description of beta-lactam antimicrobial agents, including ceftobiprole, which exhibit activity against MRSA.

Antimicrobial resistance, as noted at the beginning of this introduction, remains a significant worldwide problem. We have made considerable progress in understanding the causes and potential preventative measures that can be utilized to begin to solve this problem. The papers in this

Current Topic provide valuable insights into these areas and will be useful to both the epidemiologist as well as the clinician dealing with infections caused by multiply resistant gram-positive bacteria.

References

1. Fuller JD, McGeer A, Low DE (2005) Drug-resistant pneumococcal pneumonia: clinical relevance and approach to management. Eur J Clin Microbiol Infect Dis 24:(present issue)
2. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y (2003) Comparison of mortality associated with methicillin-resistant *Staphylococcus aureus* bacteria: a meta-analysis. Clin Infect Dis 36:53–59
3. Gould IM (2005) Control of methicillin-resistant *Staphylococcus aureus* in the UK. Eur J Clin Microbiol Infect Dis 24: (present issue)
4. Kollef MH (2005) Antibiotic management of ventilator-associated pneumonia due to antibiotic-resistant gram-positive bacterial infection. Eur J Clin Microbiol Infect Dis 24: (present issue)
5. Rice LB (2005) Antibiotics and gastrointestinal colonization by vancomycin-resistant enterococci. Eur J Clin Microbiol Infect Dis 24:(present issue)
6. Klare I, Konstabel C, Mueller-Bertling S, Werner G, Strommenger B, Kettlitz C, Borgmann S, Schulte B, Jonas D, Serr A, Fahr AM, Eigner U, Witte W (2005) Spread of ampicillin/vancomycin-resistant *Enterococcus faecium* of the epidemic-virulent clonal complex-17 carrying the *esp* and the *hyl* genes in German hospitals. Eur J Clin Microbiol Infect Dis 24:(present issue)
7. Eliopoulos GM (2005) Antimicrobials for treatment of serious infections caused by resistant *Staphylococcus aureus* and enterococci. Eur J Clin Microbiol Infect Dis 24:(present issue)