Strategies for managing today's infections

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ABSTRACT

Bacterial infections are becoming more difficult to treat. At the present time *c.* 70% of nosocomial infections are resistant to at least one antimicrobial drug that previously was effective for the causative pathogen. Pathogens that are notorious for their virulence and ability to develop resistance include *Staphylococcus aureus*, *Enterococcus* spp., members of the Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter* species. Notable resistance patterns that have emerged include methicillin resistance in *S. aureus*, which started in the healthcare setting but has now moved into the community. Vancomycin resistance in enterococci is frequently seen, and vancomycin resistance in methicillin-resistant *S. aureus* is a public health threat. Resistance patterns seen in pseudomonal and *Acinetobacter* infections are rapidly shifting. The situation has become sufficiently serious for clinical opinion leaders to call upon governments for assistance in addressing the problem. In this worsening environment, in which patients are at progressively greater risk of untreatable infections, clear recommendations for prescribers are urgently needed. Severity of infection and underlying conditions are key issues, as patients with the most serious diseases are those in most urgent need, and improvements in our ability to predict likely infecting pathogens when empirical therapy is necessary are needed. Risk-factors and local resistance patterns must be accounted for, and initial empirical therapy should be adequately broad spectrum and adequately dosed. Agents must be highly active, able to penetrate adequately to the site of infection, safe, and well-tolerated.

Keywords Bacterial infection, community-acquired, empirical therapy, methicillin-resistant *Staphylococcus aureus*, nosocomial, Panton–Valentine leukocidin, *Pseudomonas aeruginosa*, resistance, review, virulence

Clin Microbiol Infect 2008; **14** (Suppl. 3): 22–31

INTRODUCTION

Although the phenomenon of drug resistance in bacterial pathogens is not new, the high prevalence of drug-resistant highly pathogenic bacteria has been unprecedented in recent years. Data on methicillin-resistant *Staphylococcus aureus* (MRSA), a key contributor to concern about resistant pathogens, illustrate the scope of this problem. The European Antimicrobial Resistance Surveillance System (EARSS) reported in 2005 [1] on 30 countries that submitted results for MRSA. All of the southern European countries reported high levels of MRSA (eight with rates of over 40%). Four countries (Czech Republic, Slovakia, Hungary and Germany) with rates of MRSA below 10% in 2001 reported dramatic increases in 2005. Only seven (mainly northern countries) reported MRSA rates below 3%, although significant increases were reported for three of these: The Netherlands (from 0.34% – 0.93%), Denmark (0.28% – 1.7%), and Finland (0.95% – 2.91%). The only exceptions to this trend were France and Slovenia, both of which succeeded in consistently reducing proportions of methicillin-resistant isolates from 2001 to 2005. In the USA, the continuing increase in levels of staphylococcal resistance in hospitals remains a cause for concern. The proportion of isolates of *S. aureus* that were resistant to methicillin, oxacillin or nafcillin was reported as continuing to rise, and in 2004 it had reached nearly 60%. Furthermore, the hospital is not the only source of resistant pathogens, as genetically distinct MRSA strains have emerged in the community [2].

The challenge of antimicrobial resistance is not limited to MRSA. Currently, the annual incidence

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Y. Carmeli declares no conflict of interests.

of nosocomial infections due to any resistant bacterial species in the USA is *c.* 1.4 million [3].

Severe infections caused by antimicrobial resistance pose obvious treatment challenges. The aim of this article is to review trends in MRSA and other resistant pathogens associated with serious infections, to discuss the characteristics of an optimal antibiotic, and to consider strategies for managing patients infected with resistant organisms.

PATIENTS WITH SEVERE INFECTIONS

Patients with severe infections have urgent treatment needs; thus, severe infections must be identified quickly. Severity of infection is determined by three factors: (i) host (patient) characteristics, (ii) the disease or syndrome itself, and (iii) the pathogen causing the illness (species, virulence, and susceptibility to antimicrobial agents).

Populations in developed countries are ageing, and as a result, patients are increasingly elderly, more debilitated, more likely to have underlying medical conditions, and more likely to be immunosuppressed because of ageing, disease, and/or medical therapy. Increasing proportions of patients have resistant infections from institutions such as nursing homes and rehabilitation centres. Readmissions related to short hospital stays may introduce into the hospital environment large numbers of patients who have been recently treated with antibiotics [4–7].

Infectious disease syndromes that may immediately be classified as severe infection include those involving the central nervous system, bacteraemia/sepsis, hospital-acquired pneumonia, and severe soft-tissue infections. Nosocomial bloodstream infections are a major cause of death and morbidity in the USA, with an estimated quarter of a million cases annually [8]. Moreover, the numbers of such infections caused by antibiotic-resistant organisms are increasing in the USA. The nationwide Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) survey, carried out from 1995 to 2002 in 49 US hospitals recorded 24 179 nosocomial bloodstream infections, 87% of which were monomicrobial [9]. The proportion of *S. aureus* species with methicillin resistance increased from 22% in 1995 to 57% in 2001. Over the course of the survey, vancomycin resistance was seen in 2% of *Enterococcus faecalis* and 60% of *Enterococcus faecium* isolates.

PATHOGENS ASSOCIATED WITH SERIOUS INFECTIONS

MRSA

Along with the high prevalence of hospital-acquired MRSA in the USA and its increasing prevalence in other countries, the emergence of community-acquired MRSA infection is of public health concern, particularly because of the risk of transmission [10]. Community-acquired MRSA infections are now being reported in young and healthy individuals with no obvious risk-factors [11–13]. Most cases involve skin and soft-tissue infection, but life-threatening invasive infections such as necrotising pneumonia [14], necrotising fasciitis [15] and sepsis [16] are also being reported. In some areas, community-acquired MRSA infections have become more prevalent than community-acquired infections with methicillin-susceptible strains [10].

Characterisation of 117 community-acquired MRSA isolates from the USA, France, Switzerland, Australia, New Zealand and Western Samoa has identified genes that are unique to community-acquired organisms and are shared by isolates from all three continents (North America, Europe, and Oceania) [17]. These are a type IV SCC*mec* cassette (a methicillin resistance locus) and the locus for Panton–Valentine leukocidin (PVL). The PVL locus is carried on a bacteriophage and appears to represent a stable marker of community-acquired MRSA in different countries [17].

There appears to be an association between MRSA and the presence of PVL in skin and respiratory tract infections (Strauss *et al.*, 47th ICAAC, abstract K-1092; Strauss *et al.*, 17th European Congress of Clinical Microbiology and Infectious Diseases, abstract O120). In a series of 415 skin and soft-tissue infections (abscesses, wounds, or cellulitis) analysed for PVL expression, PVL-positive strains of MRSA (and methicillin-sensitive *S. aureus*) were found to be widely prevalent in deep-seated complicated skin and skin structure infections (Strauss *et al.*, 17th European Congress of Clinical Microbiology and Infectious Diseases, abstract O120). PVL expression was significantly more likely to be