Trends in Antimicrobial Resistance in Health Care–
Associated Pathogens and Effect on Treatment

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Antimicrobial resistance in health care–associated pathogens is a growing concern for health care and for public health. A recent shift in the epidemiological profile of methicillin-resistant Staphylococcus aureus has resulted not only in health care–associated infections but now, also, in community-associated infections. Reports have described S. aureus exhibiting decreased susceptibility and, even, resistance to vancomycin. The rate of vancomycin resistance among enterococci may be leveling; however, vancomycin resistance in Enterococcus faecium has already achieved high levels. Multidrug resistance in Pseudomonas aeruginosa is increasing, and carbapenem-resistant Klebsiella strains are emerging. Acinetobacter species cause a minority of health care–associated pneumonias due to gram-negative organisms, but a growing proportion is resistant to carbapenems and third-generation cephalosporins. Recent increases in the frequency and severity of Clostridium difficile–associated illness are associated with the emergence of a hypervirulent C. difficile strain with increased resistance to the fluoroquinolones. The presence of these and other resistant organisms in health care facilities limits the number of effective antimicrobials available for treatment.

There is great concern among public health authorities around the globe about the threat of increasing antimicrobial resistance [1]. In response to these concerns, medical experts, professional societies, and agencies, such as the Centers for Disease Control and Prevention (CDC), have proposed initiatives to curtail the spread of antimicrobial resistance in pathogenic bacteria [2, 3]. Although various strategies to contain the spread of antimicrobial resistance have been proposed, a better understanding of the interplay among antimicrobial use, microbial virulence, and microbial adaptation (specifically, antimicrobial resistance) is needed to determine which strategies are likely to be most effective and achievable.

Current trends in antimicrobial resistance among health care–associated (and previously health care–associated) pathogens that cause serious infections are discussed in the present article, as is the effect of resistance on the usefulness of available agents for the treatment of infections caused by antimicrobial-resistant bacteria.

GRAM-POSITIVE ORGANISMS

The history of resistance among Staphylococcus aureus isolates to various antimicrobial agents illustrates several successive evolutionary stages of resistance. Initially susceptible to penicillin G, this gram-positive coccus quickly developed the ability to produce a β-lactamase (i.e., penicillinase) that inactivated both the natural penicillins and the aminopenicillins [4]. This resistance was, at first, sporadic, but it then became more common; it was first observed in the hospital setting but later spread to the community (figure 1). Penicillin resistance in S. aureus eventually stimulated the development of several semisynthetic penicillinase-resistant agents (e.g., methicillin) [5]. Methicillin-resistant strains were first reported in the early 1960s [8]. Methicillin-resistant S. aureus (MRSA) became endemic in many hospitals during the 1980s [9, 6], and it has recently been appreciated as a cause of community-associated infections (figure 1) [7, 10].

During the past 3 decades, MRSA has created significant epidemiological, infection-control, and therapeutic management challenges. According to data from...
the National Nosocomial Infections Surveillance System (NNIS) of the CDC (which are affected by a disproportionate number of cases reported from large hospitals in the northeastern United States), the prevalence of MRSA in intensive care units (ICUs) almost doubled (from 36% to 62%) between 1992 and 2002 [6]. Although, in the 1980s, there was a definite stepwise increase in the rate of methicillin resistance among S. aureus, according to hospital size [9], this is no longer the case, with similar rates now observed in small community hospitals and large medical centers [6].

The increasing prevalence of MRSA in hospitals has led to the increased use of vancomycin for treatment [11]. Although vancomycin remains active against the majority of MRSA strains [12], infections caused by vancomycin-nonsusceptible S. aureus have been reported [13–15]. There are now 14 US isolates of vancomycin-intermediate S. aureus (VISA; MIC, 8–16 μg/mL) that have been documented by the CDC, and there are >30 isolates for which vancomycin MICs (4 μg/mL) are approaching the vancomycin MICs associated with VISA [15]. In a case-control study, recent vancomycin use and the development of MRSA infection within 2 or 3 months of development of the current infection were identified as independent risk factors for infection with VISA strains [14]. VISA appears to adapt to the presence of vancomycin through a series of mutations, resulting in strains that can overproduce cell-wall components that bind vancomycin and limit its penetration into the cell. Overall, vancomycin-nonsusceptible strains have retained susceptibility to several available agents, including linezolid and trimethoprim-sulfamethoxazole; both of these drugs, along with several other agents used in various combinations, have been used successfully in the treatment of VISA infections [15].

To date, there have been 4 reports of vancomycin-resistant S. aureus (MIC, ≥32 μg/mL), 2 from Michigan and 1 each from Pennsylvania and New York [13, 16, 17] (unpublished data). Each infection was caused by isolates with distinct PFGE patterns. Comorbid illnesses were common (e.g., 3 patients had diabetes or morbid obesity). All patients had a history of recurrent MRSA infections, had received vancomycin (2 patients had recently received vancomycin; 1 patient had received it several months before detection of vancomycin resistance, and 1 patient had received it several years before detection of vancomycin resistance), and had either a remote or concurrent history of colonization with vancomycin-resistant enterococci (VRE). There has been no evidence of transmission of vancomycin-resistant S. aureus to other patients or health care workers. All 4 isolates contained both the mecA and vanA genes, which mediate methicillin resistance and vancomycin resistance, respectively. The presence of vanA suggests that the resistance determinant was likely acquired from VRE by conjugation. In fact, in at least 2 of the 4 cases, the “donor” enterococcal isolate (i.e., the isolate donating the vanA gene) was identified [18, 19]. As with VISA isolates characterized by the CDC to date, vancomycin-resistant S. aureus isolates have remained susceptible to a number of available antimicrobials, including quinupristin/dalfopristin, trimethoprim-sulfamethoxazole, and linezolid; both of the latter 2 agents were used successfully in the treatment of 2 of the 4 infections reported to date [15]. The 2 most recently reported vancomycin-resistant S. aureus isolates were also susceptible to daptomycin, which was recently approved by the US Food and Drug Administration for the treatment of certain infections caused by S. aureus.

In addition to the recent recognition that VRE may serve as a source of genetic determinants of vancomycin resistance that can be transferred in vivo to MRSA [18, 19], VRE are, in their own right, an important cause of bloodstream, wound, and urinary tract infections in immunosuppressed and other severely ill inpatient populations. Vancomycin resistance in enterococci was first reported from Europe in 1988 [20], and it was reported soon afterward in the United States. By 1993, the prevalence of VRE had increased 20-fold in the ICUs of US hospitals [21]. According to more-recent NNIS data, the prevalence of all VRE in US ICUs leveled off (to ~28%) between 2001 and 2004; this has occurred as the prevalence of vancomycin-resistant Enterococcus faecium has leveled off (prevalence, >70%) (figure 2) [22].

Although rates of resistance appear to be stable in ICUs, VRE may be emerging as a cause of occasional infection in new patient populations, such as patients receiving hemodialysis and patients in pediatric hematology/oncology departments [15, 22]. Moreover, widespread colonization may occur in the aforementioned new patient populations, in which MRSA colonization is also prevalent, thereby increasing the opportunity for

Figure 1. Evolution of antimicrobial-resistant Staphylococcus aureus as a cause of nosocomial and, then, community-acquired infections [5–7]. Black squares, nosocomial infection; gray squares, community-acquired infection.
Outbreaks have occurred in populations with a high degree of 
transmission of genetic determinants of vancomycin resistance. 
Especially in the case of *E. faecium*, which is usually resistant 
to the penicillins, vancomycin resistance has severely limited 
the clinical armamentarium available to treat enterococcus 
infections. Fortunately, there are several newer drugs now available 
that have in vitro activity against vancomycin-resistant *E. faecium*, 
including quinupristin/dalfopristin, linezolid, fosfomycin, and daptomycin. 
The US Food and Drug Administration, on the basis of supportive clinical data, has approved 
in quinupristin/dalfopristin and linezolid for the treatment of infections 
cause by vancomycin-resistant *E. faecium*.

As previously mentioned, MRSA is an emerging pathogen 
associated with community-associated infections. Interest in 
MRSA greatly increased after the publication, in 1999, of a 
report of 4 deaths of pediatric patients that resulted from community-associated MRSA infection [10]. In contrast to health care–associated infection, MRSA infection in the community setting has been documented in patients without known risk factors for MRSA infection (e.g., recent hospitalization, recent surgery, residence in a long-term care facility, or injection drug use). The prevalence of community-associated MRSA (as a proportion of all MRSA infections) varies according to the geographic region of the country (from 9% in Maryland to 20% in Georgia) and according to race within the geographic region (prevalence, 43% and 17% among African Americans and whites, respectively, in Georgia, and 12% and 5%, respectively, in Maryland) [7]. These strains primarily cause skin and soft-tissue infections (prevalence, 77%) and, less often, traumatic wound infection (prevalence, 10%) and urinary tract infection, sinusitis, bacteremia, and pneumonia (prevalence, <5% each). Outbreaks have occurred in populations with a high degree of skin-to-skin contact (e.g., athletes, persons in correctional facilities, and military recruits) [23–25].

There is evidence to suggest that community-associated MRSA strains may increasingly cause health care–associated MRSA infections [26, 27]. Despite this early evidence of migration into the health care setting, community-associated MRSA isolates have consisted of strain types that are distinct from traditional health care–associated isolates [24, 27]. Staphylococcal cassette chromosome mec type IV is the most common determinant of resistance among the MRSA strains causing community-associated infections, which are generally less resistant to antimicrobial agents (i.e., they are more susceptible to fluoroquinolones and clindamycin) than are MRSA strains that cause health care–associated infections. Also, compared with health care–associated MRSA strains, community-associated MRSA strains are more likely to carry the genes for Panton-Valentine leukocidin toxin, which has been associated with the development of necrotizing pneumonia and necrotic abscesses [28]. Miller et al. [29] recently reported findings for 14 patients from the Los Angeles community who, during January 2003 to April 2004, presented with wound culture results that were positive for MRSA and clinical and intraoperative findings of necrotizing fasciitis, necrotizing myositis, or both. None of the patients died, but all had serious complications. All MRSA isolates belonged to the same genotype (i.e., USA 300), were mec type IV, and carried the genes for Panton-Valentine leukocidin toxin but no other toxin genes.

During the 2003–2004 US influenza season, 17 cases of community-acquired staphylococcal pneumonia were reported to the CDC; 15 of these cases were caused by MRSA [30]. These cases of pneumonia followed documented cases of influenza or influenza-like illness, and they occurred in primarily healthy patients who did not have traditional risk factors for MRSA infection. Thirteen patients had severe disease that required ICU care, and approximately one-third of these patients died. Secondary staphylococcal pneumonia occurring after influenza infection has been repeatedly observed (during the outbreaks of 1918, 1957–1958, and 1968), suggesting the potential role of particularly virulent bacterial strains in significantly affecting influenza-associated morbidity and mortality. This may be an important consideration as preparations are made for the next influenza pandemic.

The emergence of MRSA in the community has an obvious effect on choices of empirical treatment for skin and soft-tissue infections and community-acquired pneumonia. In regions where MRSA is prevalent in the community, clindamycin or trimethoprim-sulfamethoxazole has been proposed for the treatment of skin and soft-tissue infections, and incision and drainage of purulent lesions (to decrease the bacterial load and to obtain material for culture) are indicated, where possible. A change in empirical therapy for community-acquired pneumonia may need

![Figure 2. Proportion of vancomycin-resistant enterococci in intensive care unit patients [22].](image-url)
to be considered during the respiratory disease season, although doing so would increase the potential for overuse of vancomycin and newer agents with activity against MRSA.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Most attention to the emergence of antimicrobial-resistant bacteria in hospitals has been focused on gram-positive organisms for which new antimicrobial agents are available for treatment. In contrast, less attention has been focused on emerging multidrug-resistant gram-negative organisms, for which there is a current need for new antimicrobials for treatment [31]. For instance, data collected between 1994 and 2002 at one tertiary care center in the United States not only showed the emergence of multidrug-resistant Pseudomonas aeruginosa (prevalence, 1%–16%) but also showed the emergence of multidrug-resistant Klebsiella species (prevalence, 0.5%–17%) [32]. The most common resistance pattern was coresistance to quinolones, third-generation cephalosporins, and aminoglycosides. Related trends in resistance among P. aeruginosa have been observed in the national NNIS database (figure 3); among P. aeruginosa isolates recovered from ICU patients in 2003, the overall rate of resistance to carbapenems was 20%, and that of resistance to third-generation cephalosporins and quinolones was ∼30% (NNIS, unpublished data).

Acinetobacter baumannii has emerged worldwide as an important pathogen in hospitalized patients, causing high mortality rates. The organism can cause many infections, including pneumonia, bacteremia, meningitis, urinary tract infection, and skin and soft-tissue infections [33]. National data from the NNIS indicate that the prevalence of Acinetobacter organisms among gram-negative pathogens causing pneumonia in ICUs has increased from 4.2% in 1986 to 7.0% in 2003, with resistance to imipenem (increase in prevalence, from 0% to 42%) and ceftazidime (increase in prevalence, from 18% to 68%) increasing substantially during the same period (NNIS, unpublished data). The organism accounts for ∼10% of all gram-negative isolates identified in patients at military hospitals where service members injured in Afghanistan, Iraq, or Kuwait were treated (e.g., field hospitals, tertiary care centers for military personnel in the United States and abroad, and US Navy hospital ships) [34]. There have been an increasing number of multidrug-resistant A. baumannii infections identified in patients at military hospitals where service members injured in Afghanistan, Iraq, or Kuwait were treated (e.g., field hospitals, tertiary care centers for military personnel in the United States and abroad, and US Navy hospital ships) [35]. The antimicrobial resistance pattern of the A. baumannii isolates recovered in these military settings is similar to that of the multidrug-resistant strains isolated in ICUs in the United States and Europe. Although the sources of these infections are uncertain, studies of environmental sources in the field and the potential for transmission during treatment at (or departure from) military medical facilities are being investigated.

During the past 2 decades, increased utilization of cephalosporins as “workhorse” antimicrobial agents has coincided with the emergence of Enterobacteriaceae, primarily Klebsiella pneumoniae, that possess extended-spectrum β-lactamases [36]. Carbapenems have been used for the treatment of serious infections caused by isolates possessing extended-spectrum β-lactamases. Especially problematic for the clinician is the recent emergence of carbapenem-resistant Klebsiella species. Three carbapenem-hydrolyzing β-lactamase variants (KPC-1–KPC-3) have been reported [37–39]; these enzymes confer moderate- to high-level resistance to all agents in the carbapenem class. Some of the plasmids that carry the gene responsible for carbapenem resistance (blaKPC) also carry genes encoding extended-spectrum β-lactamases [40]. In addition, many of these isolates also carry determinants of resistance to aminoglycosides and are fluoroquinolone resistant [36], making these strains resistant to multiple classes of antimicrobial agents. With carbapenems being the last antimicrobial class developed for the treatment of gram-negative bacterial infections, and with the increasing prevalence of multidrug-resistant Enterobacteriaceae, there has been a resurgence in the use of the polymyxins, which, although highly active against gram-negative bacteria, were abandoned in the 1970s because of toxicity, especially nephrotoxicity [41]. However, recent experiences suggest that polymyxins can be used to treat serious infections due to multidrug-resistant gram-negative bacteria without causing significant associated adverse events, perhaps on the basis of the use of lower doses, avoidance of concurrent use of nephrotoxins, and improved fluid supplementation and supportive treatment [42].

CLOSTRIDIUM DIFFICILE

Although the association of an emerging epidemic of Clostridium difficile-associated disease (CDAD) with the effect of an-
Multidrug-resistant C. difficile is one of the main causes of CDAD. In a recent national survey of infectious diseases clinicians, nearly 40% reported noting an increased severity of CDAD in their patient populations [46]. Other reports suggest increasing severity of CDAD. In a review of 2334 hospitalized patients with C. difficile colitis, conducted from 1989 to 2000, Dallal et al. [45] found that the incidence of illness accompanied by life-threatening symptoms increased from 1.6% to 3.2% during the 11-year study. Some patients required a colectomy (n = 44), and others died as a direct consequence of their C. difficile colitis (n = 20). In a recent national survey of infectious diseases clinicians, nearly 40% reported noting an increased severity of CDAD in their patient populations [46].

Outbreaks of CDAD between 2000 and 2004 were caused primarily by a single strain, identified by PFGE and other molecular methods, that appears to have been present in US hospitals during the 1990s [43]. More alarming are National Center for Health Statistics data that suggest that the rate of C. difficile-associated infections in US hospitals increased by 26% in 2001, compared with rates noted in 1998–2000 [44].

The effect of resistance may extend farther, because it now appears that cases of CDAD caused by the epidemic strain are less responsive to treatment with metronidazole, compared with cases treated with oral vancomycin [50, 51]. Because there is no evidence of in vitro metronidazole resistance, this apparent decrease in the efficacy of metronidazole may be the result of the increased virulence of the epidemic strain resulting in more-severe disease, which has always been better managed with vancomycin than with metronidazole [51]. Thus, widespread use of one class of antimicrobial agents (the fluoroquinolones) may have promoted dissemination of a more virulent strain of C. difficile, which, in turn, is now resulting in an increased need for oral vancomycin for its management. It remains to be determined whether increased use of oral vancomycin for the treatment of severe CDAD caused by the epidemic strain will unfavorably affect the fairly stable prevalence of VRE that we have observed in US hospitals of late. A relationship between infection or colonization with C. difficile and the emergence of VRE has already been reported elsewhere [52, 53].

CONCLUSION

An effective strategy to limit the effect of multidrug resistance must be multifaceted and must include education of patients and physicians about appropriate antimicrobial use, use of effective infection-control practices to prevent transmission from infected to uninfected patients, surveillance of antimicrobial resistance and antimicrobial use, improved use of immunization, and development of alternative therapies that may, in some cases, circumvent the need for antimicrobial therapy. Specific measures are being taken by the CDC, as part of an overall public health response to control multidrug-resistant organisms; such measures include the revision of isolation guidelines, which are currently undergoing review. In addition, there are ongoing campaigns designed to educate the public and the health care community about the dangers of antimicrobial resistance and what may be done to control it. These campaigns include the “Get Smart” program, which primarily focuses on outpatients [54], and the 12-step Campaign to Prevent Antimicrobial Resistance in Healthcare Settings [55]. However, regardless of the strength of present-day control strategies, the battle to control antimicrobial resistance will remain with us as long as we must rely on these drugs as our primary means of treating infections.

Acknowledgment


References

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