



Antimicrobial Resistance in Gram-Positive Bacteria

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ABSTRACT

Gram-positive bacteria are common causes of bloodstream and other infections in hospitalized patients in the United States, and the percentage of nosocomial bloodstream infections caused by antibiotic-resistant gram-positive bacteria is increasing. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are of particular concern. In the United States, approximately 60% of staphylococcal infections in the intensive care unit are now caused by MRSA, and percentages continue to rise. Outbreaks of hospital-acquired MRSA (HA-MRSA) are typically the result of clonal spread by MRSA being transferred from patient to patient, frequently using healthcare personnel as intermediaries. HA-MRSA strains are generally multidrug resistant. Vancomycin is the standard treatment for serious MRSA infections, but a few cases of vancomycin-resistant *S aureus* (VRSA) have recently emerged in the United States. Community-acquired MRSA (CA-MRSA) is also increasing. Soft tissue infections are the most frequent presentations of CA-MRSA, but life-threatening invasive infections occur as well, including necrotizing pneumonia. The mechanisms of methicillin resistance are the same for CA-MRSA and HA-MRSA, but susceptibilities to non- β -lactam antibiotics often differ. CA-MRSA exhibits broader antibiotic susceptibility than does HA-MRSA. The proportion of enterococci resistant to vancomycin continues to rise in the hospital setting, with the overwhelming majority of infections due to *Enterococcus faecium*. Clonal spread of VRE has been documented, but polyclonal outbreaks associated with antimicrobial use are also common. The relations between antibiotic use and VRE colonization are complex and related to the antienterococcal activity, biliary excretion, and antianaerobic activity of the antibiotic. Recent results show a decline in invasive pneumococcal disease (IPD) since the introduction of 7-valent pneumococcal conjugate vaccine, and suggest that, where available, vaccines may be useful in the battle to slow the spread of resistant gram-positive cocci. © 2006 by the Association for Professionals in Infection Control and Epidemiology, Inc. and Elsevier Inc. All rights reserved.

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Gram-positive bacteria—particularly gram-positive cocci like coagulase-negative staphylococci, *Staphylococcus aureus*, and *Enterococcus* spp—are extremely important pathogens in the hospital environment. Data from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) project, which monitors significant bloodstream infections in hospitalized patients in the United

States, indicated that 60% of nosocomial bloodstream infections for the 3-year period from April 1995 through April 1998 involved gram-positive bacteria.¹ Coagulase-negative staphylococci were the causes of 31.9% of monomicrobial nosocomial bloodstream infections, followed by *S aureus* in 15.7%, enterococci species in 11.1%, and viridans streptococci in 1%. Updated figures from the SCOPE project covering March 1995 through September 2002 revealed similar findings.² Although the percentage of nosocomial bloodstream infections caused by gram-negative bacteria has remained approximately constant for the overall and pediatric populations over the years covered by the SCOPE

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project, the percentage of species resistant to standard antibiotics has increased,^{2,3} and increasing resistance in gram-positive bacteria can be expected to complicate treatment and potentially lead to increased morbidity and mortality.

This article takes a closer look at the emergence and spread of methicillin-resistant *S aureus* (MRSA) in the hospital and community settings, as well as initial cases of *S aureus* with intermediate or, more recently, high-level resistance to vancomycin. The emergence and spread of vancomycin-resistant enterococci (VRE) are also examined, as is the potential relevance of VRE for emergence of vancomycin-resistant *S aureus* (VRSA). Last, attention is focused on the potential role of vaccines in reducing the occurrence of penicillin- and multi-drug-resistant pneumococci.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Virtually all *S aureus* strains were susceptible to penicillin G when the latter was initially introduced in the early 1940s, but by 1944 the first reports of penicillin-resistant *S aureus* had already appeared, and today virtually all strains of *S aureus* are resistant to natural penicillins, aminopenicillins, and antipseudomonal penicillins.^{4,5} Resistance to these drugs occurs because of the acquisition of genes that encode drug-inactivating enzymes, initially known as penicillinases and now called β -lactamases. At first, cases of penicillin-resistant *S aureus* were limited and appeared only in health-care settings, but over time resistant species were observed and became increasingly prevalent in the wider community as well.⁴ Methicillin and other penicillinase-resistant penicillins were developed to treat infections caused by penicillin-resistant *S aureus* and met with initial success. However, over time strains of methicillin-resistant *S aureus* (MRSA) began to appear and to spread—first within the hospital setting and more recently within the community, in many ways paralleling the earlier emergence and spread of penicillin-resistant *S aureus*.

Hospital-Acquired MRSA and the Emergence of Vancomycin-Resistant Strains

Methicillin was introduced in Europe in 1959 and in the United States in 1961, and the first cases of MRSA were reported in the United Kingdom in 1961, followed soon thereafter by reports in other European countries, Japan, and Australia.⁶ The first report of MRSA in the United States appeared in 1968.⁷ Periodic outbreaks of MRSA were observed in various countries throughout the 1970s and were typically associated with high methicillin use in intensive care units (ICUs),⁶ but it was not until the 1980s that MRSA began to become a really significant problem in United States hospitals—first in hospitals with a large number of beds and then in community hospitals.⁸

MRSA is currently recognized as a major problem in hospitals and the broader community in the United States and throughout the world.⁹ In the United States, the Na-

tional Nosocomial Infections Surveillance (NNIS) system report for 2004 identified methicillin resistance in 59.5% of *S aureus* infections in ICU patients.¹⁰ This represented an 11% increase in resistance compared with rates for the period 1998 to 2002. The most recent SCOPE project report showed that methicillin resistance was present in 44% of *S aureus* bloodstream isolates from ICU infections.² Moreover, a trend analysis showed a significant increase in the proportion of *S aureus* isolates resistant to methicillin from 1995 to 2001 (22% vs. 57%; $P < 0.001$). In hospitalized pediatric patients with staphylococcal bloodstream infection, the proportion expressing methicillin resistance increased from 10% in 1995 to 29% in 2001.³

Nosocomial MRSA is remarkable for its clonal pattern of spread. A recent study looking at 359 MRSA isolates collected from 20 countries from 1961 to 1999 identified 11 major MRSA clones within 5 groups of related genotypes.¹¹ Similarly, Oliveira and colleagues¹² used molecular-typing techniques to identify 5 major MRSA clones that accounted for approximately 70% of >3,000 MRSA isolates obtained primarily from hospitals in the United States, South America, and Europe. The major mover of this sort of clonal spread is thought to be infection control lapses by healthcare practitioners—physicians, nurses, or other persons who become colonized with *S aureus* and then have contact with hospitalized patients.¹³ MRSA, like any *S aureus*, is known to colonize the skin and particularly the anterior nares⁴; such colonization may be transient or persistent,^{4,13} and may spread faster during times of upper respiratory tract viral infections.¹⁴

In general, nosocomial MRSA is multidrug resistant. Expression of the *mecA* gene encoding low-affinity penicillin-binding protein PBP2a confers resistance to other β -lactams in addition to methicillin,¹⁵ but the resistance pattern of MRSA typically includes other classes of antibiotics as well. Results from a recent study in the United Kingdom examining a new epidemic strain of MRSA, designated EMRSA-17, illustrate this multidrug resistance.¹⁶ EMRSA-17 expressed resistance to methicillin, fluoroquinolones (ciprofloxacin), macrolides (erythromycin), aminoglycosides (gentamicin, kanamycin, neomycin, and streptomycin), tetracycline, rifampin, and fusidic acid. Virtually all variants of this strain were multidrug resistant. Borderline resistance was also noted for teicoplanin, a glycopeptide available in the United Kingdom but not the United States.

In particular, fluoroquinolone resistance is a hallmark of nosocomial MRSA, although this was not always the case. When ciprofloxacin was first licensed, it was recommended as the first orally administered treatment effective against MRSA. However, within 1 year many hospitals observed dramatic increases in the rate of ciprofloxacin resistance in MRSA. In 1 study, high-level ciprofloxacin resistance was observed within 3 months of ciprofloxacin introduction, and within 1 year, 79% of all MRSA from hospitalized patients exhibited resistance.¹⁷ Ciprofloxacin resistance in methicillin-susceptible *S aureus* (MSSA) increased from 0% to

13.6% over the same period. Exposure to either ciprofloxacin or levofloxacin has been shown to increase the risk for MRSA but not MSSA in hospitalized patients.¹⁸

For many years, vancomycin was the only effective treatment for serious MRSA infections. But in the past 4 years, 4 new agents with anti-MRSA activity have been introduced (quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline). These new agents are most welcome, since the past decade has seen the emergence of vancomycin resistance in *S aureus*. *S aureus* with intermediate resistance to vancomycin (vancomycin-intermediate *S aureus* [VISA]; minimum inhibitory concentration [MIC], 8 to 16 mg/L) was first observed in 1996 in a strain isolated from a hospitalized patient in Japan.¹⁹ In the United States, the first 4 cases of VISA were reported between 1997 and 1999.^{20–22} In each instance, emergence of VISA was associated with extensive exposure to vancomycin, ranging from 25 days²¹ to 18 weeks.²⁰ These were patients, often on dialysis, who were exposed to large amounts of vancomycin to treat MRSA infections.

The mechanism of resistance in VISA has been linked to cell wall thickening, which may cause vancomycin molecules to become trapped in the outer layers of the cell wall, thereby limiting access to the cytoplasmic membrane where the functional targets of vancomycin are located.²³ It should be noted that even among more susceptible strains, there are subpopulations that emerge resistant to vancomycin or at least intermediately susceptible after vancomycin exposure, associated again with an increase in the size of the cell wall. More recently, strains fully resistant to vancomycin or VRSA (MIC, 64 mg/L) were isolated from 3 patients in the United States.^{24–27} The mechanism for this high-level vancomycin resistance involves the horizontal transfer of a transposon containing *vanA* and associated genes from VRE.

Community-Acquired MRSA

Initially, MRSA was observed only in the hospital setting, but it is now clear that MRSA may be acquired in the community as well. In the United States, several instances of community-acquired MRSA (CA-MRSA) were reported in the upper Midwest in the early 1980s, but many of those early cases involved illegal-drug users or individuals with serious underlying disease or previous hospitalization.^{28–30} However, it is now apparent that CA-MRSA infections can occur in individuals without identifiable risk factors and that the prevalence of CA-MRSA is increasing.³¹ The exact prevalence of CA-MRSA has been difficult to determine, but it appears to be increasing, particularly in children,^{32,33} and CA-MRSA is now recognized as a growing problem worldwide.³⁴

CA-MRSA infections are commonly observed in children and young adults, although older adults may also be affected. Clusters of CA-MRSA infections have been reported in correctional facilities and athletic teams.^{35–37} Skin and soft tissue infections are the most common manifestations of CA-MRSA, and furunculosis is the most frequently

reported presentation.³² CA-MRSA may also be associated with life-threatening invasive infections, including necrotizing pneumonia. The potential seriousness of CA-MRSA was first highlighted in the late 1990s, when 4 children infected with CA-MRSA died, 2 of them with necrotizing pneumonia and severe sepsis.³⁸ A high percentage of CA-MRSA strains carry genes for Panton-Valentine leukocidin, a cytotoxin that causes leukocyte destruction and tissue necrosis. Lina and colleagues³⁹ screened isolates from patients in France with *S aureus*-associated infections and identified Panton-Valentine leukocidin in 93% of the cases of furunculosis and 85% of the cases of community-acquired necrotic hemorrhagic pneumonia. More recently, Francis and coworkers⁴⁰ described 4 cases of previously healthy adult patients in the United States who developed severe necrotizing pneumonia caused by MRSA-carrying Panton-Valentine leukocidin genes. One patient died after 2 days, while the other 3 survived. All of the survivors experienced very prolonged hospitalizations, and 2 had substantial ongoing morbidity related to their infection.

Besides being acquired in the community, there are a number of other differences between CA-MRSA and hospital-acquired MRSA (HA-MRSA). Both CA-MRSA and HA-MRSA are resistant to methicillin and other β -lactams due to the presence of the *mecA* gene. However, the genetic environment of the *mecA* gene differs in hospital-acquired and community-acquired isolates. The *mecA* gene, which encodes for PBP2a, is carried on a mobile genetic element known as the staphylococcal chromosomal cassette (SCC) *mec*.³² There are 4 types of SCC*mec*, designated I–IV, which differ in size and the presence of additional resistance genes. SCC*mec* types I, II, and III are relatively large (>30 kb) and contain significant quantities of DNA in addition to the basic components of *mecA*, its regulators, and the *ccrAB* genes that confer mobility. In some cases, the functions encoded by the additional DNA are unknown; in other instances, further antimicrobial resistance determinants are included through the insertion of small plasmids or transposons. In contrast, type IV SCC*mec* is relatively small, containing little else than the basic components of SCC*mec*. Type IV SCC*mec*—roughly 20-kb long—is a typical feature of the CA-MRSA genome, compared with the SCC*mec* mobile genetic elements prevalent in HA-MRSA strains (34 to 67 kb). The small size and lack of resistance genes besides *mecA* have been implicated in the nonmultiresistant nature of CA-MRSA,⁴¹ whose drug-susceptibility profile is characterized by resistance to methicillin and other β -lactam drugs but by susceptibility to non- β -lactam drugs. However, there are exceptions, and some CA-MRSA strains exhibit resistance to a few non- β -lactam drugs as well, probably due to the acquisition of resistance via other mechanisms⁴² (Table 1). CA-MRSA strains have also been shown to multiply much more rapidly than HA-MRSA strains.⁴¹

The rapid spread and polyclonal nature of CA-MRSA has raised the intriguing question of whether methicillin

Table 1 Community-acquired methicillin-resistant *Staphylococcus aureus* antibiotic susceptibilities in 45 samples

Antibacterial Agent	Samples, n (%)		
	Susceptible	Resistant	Intermediate
Vancomycin	45 (100)	—	—
Rifampin	41 (91.1)	4 (8.9)	—
TMP-SMX	45 (100)	—	—
Tetracycline	45 (100)	—	—
Ciprofloxacin	29 (64.4)	7 (15.6)	9 (20.0)
Linezolid	45 (100)	—	—
Clindamycin*	43 (95.6)	2 (4.4)	—
Erythromycin	9 (20)	36 (80)	—
Daptomycin†	45 (100)	—	—

TMP-SMX = trimethoprim-sulfamethoxazole.

*A total of 8 isolates (18.6%) demonstrated inducible resistance.

†According to the manufacturer, ≥ 16 -mm zone is considered susceptible.

Adapted with permission from *Clin Infect Dis*.⁴²

resistance is transferable from these strains. The small size of type IV SCCmec would allow its incorporation into a bacteriophage head (an option not available to the larger versions of SCCmec), raising the possibility that transduction could be responsible for spread of the determinant between different strains. Transfer has yet to be demonstrated experimentally. Studies have shown that the presence of type IV SCCmec in CA-MRSA is the only thing that distinguishes it from community-acquired MSSA,⁴³ suggesting CA-MRSA may occur in the community when type IV SCCmec is transferred into MSSA. Compared with MSSA, CA-MRSA is more virulent. Only 3% of subjects in a prospective observational study who were colonized with MSSA at study onset went on to develop clinical infections over the next 8 to 10 weeks, compared with an infection rate of 38% in subjects originally colonized with CA-MRSA.⁴² These and other data suggest that CA-MRSA strains are much more likely to cause infection once they colonize an individual.

In summary, CA-MRSA strains are more susceptible to other antibacterial drugs than are strains of HA-MRSA. They tend to be more susceptible than hospital strains to tetracyclines, trimethoprim-sulfamethoxazole, and in some cases, clindamycin and ciprofloxacin, although there are pockets where ciprofloxacin resistance is becoming prevalent in these strains as well. These strains are different from the hospital strains in that they tend to cause infections at a higher rate, and some of these infections can be quite severe.

MULTIDRUG-RESISTANT ENTEROCOCCAL SPECIES

Despite the fact that vancomycin has been in clinical use since the late 1950s, VRE were not observed until the mid-1980s, and in the United States, VRE were virtually nonexistent as recently as 1989 (Figure 1).⁴⁴ During the

1990s, however, a dramatic rise in VRE occurred—first in ICUs, then essentially throughout hospitals. The latest NNIS report indicated that nearly 30% of all enterococci isolated from patients infected in ICUs are now resistant to vancomycin.¹⁰

Perhaps an even more remarkable aspect of this outbreak is the fact that an overwhelming majority of VRE are *Enterococcus faecium*. The Surveillance Network Database—USA showed that resistance to both vancomycin and ampicillin was much more prevalent among *E faecium* than among *Enterococcus faecalis* in patients with nosocomial bloodstream infections in 1995 and 1997.⁴⁵ By way of comparison, 94.5% of *E faecalis* were susceptible to both vancomycin and ampicillin versus only 25.4% of *E faecium*. *E faecalis* strains tend to be susceptible to ampicillin even if they express vancomycin resistance. This study also showed progressive increases in the percentage of *E faecium* strains exhibiting vancomycin resistance, from 26.2% in 1995 to 39.2% in 1996 to 48.8% in 1997. For the same years, vancomycin resistance was observed in 1.9%, 1.3%, and 1.4%, respectively, of *E faecalis* strains. More recent results from surveillance studies indicate that the proportion of *E faecium* resistant to vancomycin (*E faecium* still represents the vast majority of VRE strains) continues to rise in patients hospitalized in the United States, approaching 70% in the most recent reports.^{2,46}

Vancomycin resistance is mediated by either of 2 classes of related gene clusters: 1 class contains *vanA* and 1 class contains *vanB*.⁴⁷ Both produce resistance by altering the target for vancomycin from D-alanine-D-alanine to D-alanine-D-lactate.

A decade and a half of looking at and controlling VRE has now passed. Based on a number of hospital outbreaks of VRE and on measures taken to control them, both the Centers for Disease Control and Prevention's (CDC) Healthcare Infection Control Practices Advisory Committee

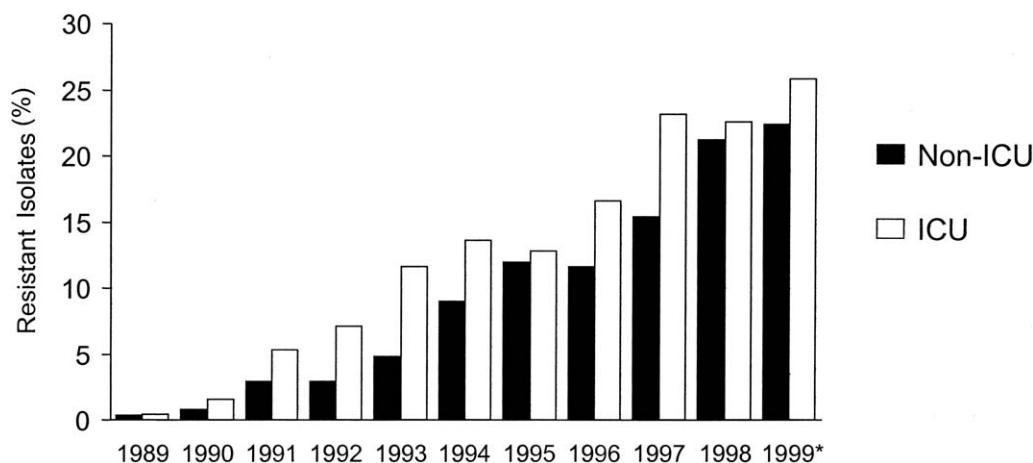


Figure 1 Emergence of vancomycin resistance in enterococci. ICU = intensive-care unit. *Results through June 1999. (Reprinted with permission from *Infect Control Hosp Epidemiol.*⁴⁴)

(HICPAC) and the Society for Healthcare Epidemiology of America (SHEA) have developed practice guidelines to prevent nosocomial transmission of VRE.^{48,49}

Two studies illustrate the kinds of outbreaks that led to current infection control guidelines. Both outbreaks were clonal and occurred in Miriam Hospital in Rhode Island. The first involved 37 patients seen in 1991 to 1992 with *vanB*-type VRE,⁵⁰ while the second involved 9 patients seen in 1994 with *vanA*-type VRE.⁵¹ In each case, the outbreak was aborted after institution of precautions that included the use of gowns and gloves by those in contact with infected or colonized patients. During the first outbreak, hospital personnel initially tried to control the outbreak by use of gloves and patient isolation, but it was only when gowns were added to the precautions that the outbreak was effectively stopped. The quick control of the second outbreak was attributed to the rapid initial institution of use of gowns and gloves and patient isolation. The findings from these studies, and others like them, led to the development of the 1994 HICPAC guidelines, which recommended patient isolation, cohorting staff who provide regular patient care, gowns and gloves, and hand washing to prevent patient-to-patient transmission of VRE. The guidelines also recommended the use of active surveillance cultures to identify the reservoir for spread and the use of good antibiotic stewardship, particularly as it relates to vancomycin use.

Unfortunately, it did not take long before some other studies showed quite different results. For example, at the University of Maryland Medical Center, a point-prevalence survey for VRE colonization showed that 16.9% of patients on the wards were colonized.⁵² In response, vancomycin use became restricted, and the HICPAC recommendations were instituted. Despite these precautions, point-prevalence surveys performed approximately 1 year later showed that the rates of VRE colonization had remained unchanged or had even slightly increased (18.7%). The reason for the negative findings, compared with the positive results from earlier studies, probably is because the outbreak at the Maryland medical center was not clonal, whereas those that occurred

at Miriam Hospital and at other hospitals reporting effective control with these precautions were clonal. When pulsed-field gel electrophoresis was used to examine 85 VRE isolates from the Maryland study, 45 distinct patterns were identified. So, in fact, the problem was greater than the spread of a single strain around the hospital, which one might reasonably hope to contain by strict infection control procedures.

In cases in which poor infection control is not the cause of a VRE outbreak, selective pressures exerted by antimicrobial use are most likely to be involved. This raises the question of which antibiotics are associated with vancomycin-resistant enterococcal colonization and infection. Several antibiotics and antibiotic classes have been associated with colonization or infection by VRE in clinical studies, including extended-spectrum cephalosporins and agents with potent activity against anaerobic bacteria.⁵³ In the 1990s, we looked at the relation between vancomycin purchases and VRE infection (defined as isolation of VRE from a normally sterile site) in 5 hospitals in the greater Cleveland area and found no association between hospital purchases of vancomycin and clinical infection rates with VRE.⁵⁴ The results did show, however, a statistically significant association between whether hospitals purchased large quantities of the β -lactam- β -lactam inhibitor combination ticarcillin-clavulanate and VRE ($P = 0.005$). There was also a nonsignificant trend toward a positive association between purchase of third-generation cephalosporins and VRE ($P = 0.188$), and there was a nonsignificant negative trend between purchases of piperacillin-tazobactam, ampicillin-sulbactam, and piperacillin together and VRE, suggesting that these penicillins may protect against VRE colonization ($P = 0.188$).⁵⁴

We used an animal model to further examine the relation between antibiotic use and VRE colonization. In the model, VRE was established in the gastrointestinal tract by gavage of large numbers of organisms (about 10^6 colony-forming units) from mice fed by water supplemented by vancomycin.⁵⁵ In this model, large quantities of VRE were present in

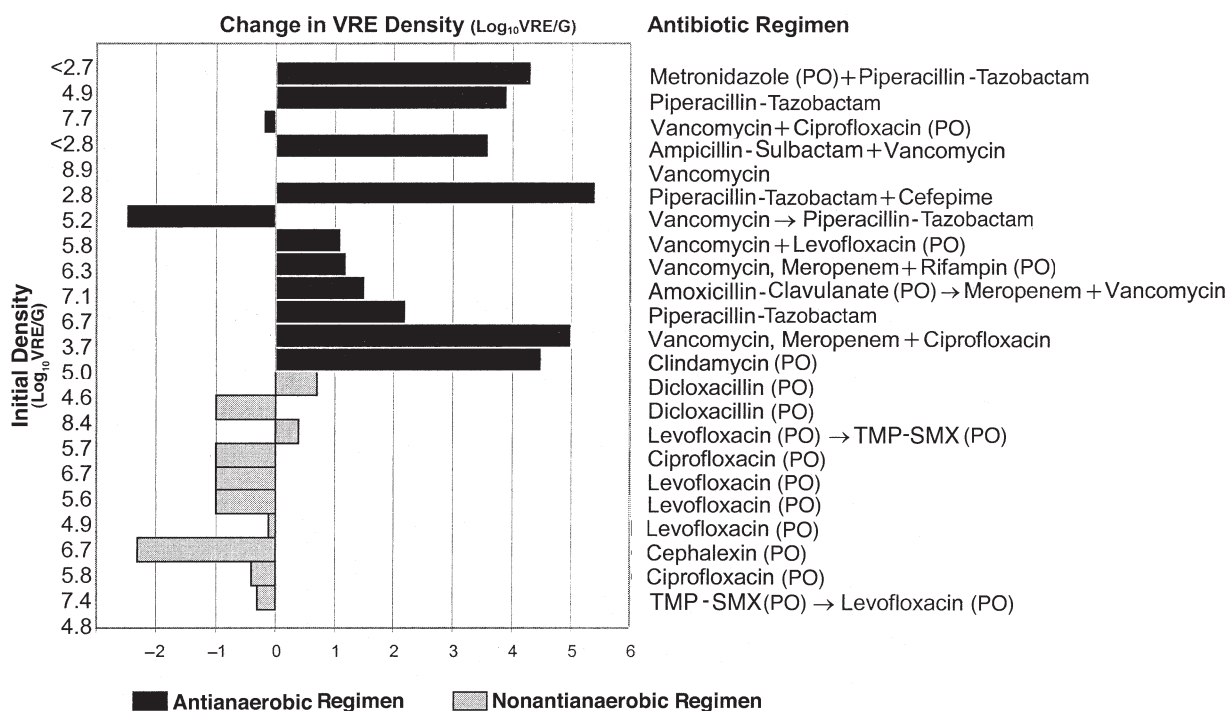


Figure 2 Change in vancomycin-resistant enterococci (VRE) density based on antibiotic drug use. The zero point represents the level of colonization at the time the antibiotic dose was given postdischarge. TMP-SMX = trimethoprim-sulfamethoxazole. (Reprinted with permission from *N Engl J Med*.⁵⁶)

the mouse feces as long as oral vancomycin was given, but VRE fecal counts decreased to below the detectable range by 3 weeks after oral vancomycin was discontinued. After vancomycin discontinuation, various antibiotic agents were administered subcutaneously to determine whether they would promote persistent high levels of stool VRE. Surprisingly, and in contrast to the clinical study mentioned earlier, ampicillin-sulbactam and piperacillin-tazobactam were associated with persistent high levels of VRE colonization. Other agents associated with persistent high-level VRE colonization included cefoxitin, clindamycin, metronidazole, ticarcillin-clavulanate, and subcutaneous or oral vancomycin. There was no association between administration of the extended-spectrum cephalosporin cefepime, ciprofloxacin, aztreonam, or saline and persistent VRE colonization.⁵⁵ Results associated with administration of ceftriaxone or ampicillin were mixed. What is noteworthy about these findings is that all of the antibiotics associated with persistence of high levels of VRE colonization have potent activity against anaerobic bacteria. These observations were extended to the clinical setting by obtaining periodic posthospital fecal cultures from patients determined to be colonized with VRE while in the hospital and then determining the patients' subsequent level of colonization after discharge.⁵⁶ In a 7-month prospective study of patients who were colonized with VRE, the density of VRE in stool during and after therapy with antibiotic regimens showed that a patient colonized in the gastrointestinal tract with VRE who received an antibiotic regimen potent against anaerobes was likely to show increases in VRE

colonization (**Figure 2**), suggesting that limiting the use of antianaerobic antibiotics in these patients may minimize the level and duration of colonization by these organisms.⁵⁶ This study also has important infection control implications in that VRE could be found on surfaces in the room if the colony counts in the stool were >10⁴ colony-forming units per gram of stool, but not if the counts were less than that.

The aforementioned studies addressed the persistence of colonization in patients already colonized, but what about establishment of colonization in the first place? Again, that question was addressed by turning to a mouse model. In this case, the goal was to colonize the gastrointestinal tract of mice with 10² colony-forming units of VRE. Stool colony counts were determined for a subset of mice prior to any intervention and on day 0, after receiving subcutaneous ceftriaxone, ticarcillin-clavulanate, piperacillin-tazobactam, or saline for 2 days before inoculation with oral VRE.⁵⁷ Ceftriaxone and ticarcillin-clavulanate were chosen because they have minimal activity against the VRE strain compared with the modest efficacy of piperacillin-tazobactam. The results showed that animals treated with ceftriaxone or ticarcillin-clavulanate established high-level colonization, whereas the animals treated with piperacillin-tazobactam or saline were not heavily colonized. The apparent protection of piperacillin-tazobactam against establishment of VRE colonization was overcome only when the VRE inoculum was increased to 1 million organisms. Therefore, the protective effect of piperacillin-tazobactam may have been related to its modest activity against VRE, combined with

substantial biliary excretion of piperacillin, which together may have led to sufficient inhibition of VRE growth in the upper gastrointestinal tract to prevent high-level colonization.⁵⁷

Taken together, the results from the studies reviewed here suggest that establishment of colonization is promoted by certain antibiotics, while other antibiotics promote persistence of colonization already established. Some antibiotics, such as ticarcillin-clavulanate, promote both establishment and persistence. Some of the factors that appear to be involved include the intrinsic activity of the different agents against VRE, excretion in bile, and potency against anaerobic bacteria. The next logical question is whether cephalosporins that differ in these respects also differ in their ability to promote establishment of VRE colonization. Turning again to the mouse model, we showed that cephalosporins that (1) do not have significant antienterococcal activity and (2) are not secreted into human bile at high concentrations (cefazolin, cefepime, and to a lesser extent ceftazidime) do not promote significant VRE colonization.⁵⁸ Conversely, cephalosporins that lack significant antienterococcal activity but are secreted into human bile at high concentrations (ceftriaxone and cefotetan) were associated with high-level colonization. In summary, it appears that the effect of various antibiotics on VRE colonization is complex; it is related to antienterococcal activity, biliary excretion, and activity against anaerobes. One cannot simply say that a particular antibiotic class promotes VRE colonization.

PENICILLIN-RESISTANT PNEUMOCOCCI AND VACCINES

Penicillin resistance is common in *Streptococcus pneumoniae*, and many strains of *S pneumoniae* are resistant to other antibiotics as well.⁵⁹ Resistance has been linked to use of several different antibiotic classes. Invasive disease caused by antibiotic-resistant *S pneumoniae* is a particular concern, and the incidence of invasive *S pneumoniae* infections in the United States is highest among children aged <2 years.⁶⁰ To address these concerns, a 7-valent pneumococcal conjugate vaccine (PCV7) was developed and became approved for use in infants and young children in the United States in 2000.⁶¹ This conjugate vaccine was designed to cover the 7 serotypes most commonly occurring in United States children with invasive pneumococcal disease (IPD) and most commonly associated with drug-resistant strains.

The good news is that a number of studies have now reported that IPD rates have declined since the introduction of PCV7, including rates of disease associated with antibiotic-resistant or nonsusceptible strains of *S pneumoniae*.^{62–64} For example, among children aged <2 years, IPD rates were reported to have decreased significantly from 235 cases per 100,000 in 1999 to 46 cases per 100,000 in 2002, 2 years after PCV7 licensure

($P < 0.001$).⁶² There was also a significant decline in the proportion of IPD cases associated with penicillin-nonsusceptible pneumococcal species in this age group—from 59.8% in 1999 to 30.4% in 2002 ($P < 0.01$). The impact of the vaccine was greatest in children who received the vaccine, but there was a positive impact in older patients as well.⁶² Rates of IPD due to PCV-associated serotypes declined in all age groups after PCV7 introduction. These findings are encouraging because they indicate that there are many ways to fight antibiotic resistance and that vaccines, when they are available and effective, may be useful in the fight.

SUMMARY

Antibiotic resistance in gram-positive cocci is a persistent problem. Both infection control and antibiotic selective pressure are important factors in its spread. In some cases, as with HA-MRSA, infection control measures appear to be the most important mechanisms for limiting spread. In others, such as VRE, both infection control and antimicrobial exposures are important. Unfortunately, different antibiotics may exert different effects depending on the preexisting colonization state of the patient. Multipronged efforts, perhaps with altered emphases for different bacteria, are required to limit the spread of resistance. New antibacterial agents effective for treating serious gram-positive infections would also be welcome.

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