Editorial

Vancomycin-Resistant *Enterococcus faecium*: Headline News

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Enterococci are not particularly virulent microorganisms. True, they have a special tropism for cardiac valves and can cause infections at virtually any anatomic site in patients of all ages.[1] However, as reviewed recently by Maki and Agger,[2] they usually need help from other microorganisms. For example, although enterococci are present in high numbers when bowel contents leak into the peritoneum, antibiotic regimens that have specific anti-enterococcal activity are not required to prevent infection. In experimental models, intraperitoneal inoculation of enterococccci does not produce abscesses, peritonitis, or bloodstream infection without concomitant inoculation of other bacteria or microbial adjuvants. Shin and soft tissue infections are very rarely associated with a pure culture of enterococci. When enterococci are isolated from blood cultures, other bacteria are present as well in 24% to 45% of cases, and metastatic suppurative infections are uncommon. Compared with other bacteria normally found in the stool, such as *Escherichia coli*, enterococci are rarely (<5% of cases) recovered from urinary tract infections in otherwise healthy women with normal urinary tract anatomy. Specific enterococcal virulence factors remain to be identified and characterized.

Nonetheless, enterococci are adapted perfectly to cause trouble in the patients who fill today's hospital wards-the very old and the prematurely born, the severely ill and the immunosuppressed; patients whose host defenses have been bypassed by invasive medical devices or compromised by aggressive surgery, and those whose normal microbial flora has been altered by antimicrobial therapy. Enterococci can be recovered from mouth to anus in many patients, but these bile-resistant organisms favor the colon where they have a secure ecological niche. ***Enterococcus faecalis*** is present in concentrations of 10^5-10^7 colony-forming units (CFU)/g of feces in almost 100% of individuals, and ***E faecium*** is present in slightly lower concentrations in approximately 25%; the other ten enterococcal species are found much less commonly, although almost all are capable of producing infection. Enterococci are relatively hardy microorganisms (resistant to heating at 62°C for 30 minutes, for example), and have been recovered from environmental cultures during a number of outbreak investigations. A recent epidemic of vancomycin-resistant ***Enterococcus faecium*** was attributed to persistence of bacteria on rectal probe handles of electronic thermometers.[3]

Enterococci also survive well on the hands. When fingers of volunteers were inoculated with 10^4 CFU of vancomycin-resistant ***E faecium***, more than 10^3 CFU could be recovered after 30 minutes, and handwashing with bland soap failed to eradicate the test strain.[4] Not surprisingly, hand cultures of some hospital personnel obtained during the investigation of enterococcal outbreaks have been positive. Enterococci even can colonize the gastrointestinal tract of caregivers.[5,6] In an outbreak of penicillin-resistant *E faecalis* on the infant/toddler ward of my institution, for example, the epidemic strain was recovered from the

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stool of 8 of 33 employees,[5] and colonization was associated strongly with nail biting (unpublished data). Care by one nurse, who had chronic colonization of the gastrointestinal tract, was an important independent risk factor for colonization of children.

While other potential nosocomial pathogens are present in high concentrations in the normal gastrointestinal tract, can be transmitted from patient-to-patient on the hands of caregivers, and survive well in the environment, enterococci have an additional important advantage-they are intrinsically resistant to many of the antibiotics that are used commonly in hospitalized patients.[1,7,8] Enterococci, especially *E faecium,* are relatively resistant to penicillin and are highly resistant to semisynthetic antistaphylococcal penicillins, such as oxacillin, and cephalosporins. In addition, enterococci are tolerant to all β-lactams, including the carbapenem imipenem, and have minimum bactericidal concentrations (MBCs) many-fold higher than their minimum inhibitory concentrations (MICs). They have intrinsic moderate levels of resistance to clindamycin, as well as low-level resistance to aminoglycosides. There is controversy regarding the in vitro versus in vivo activity of trimethoprim/sulfamethoxasole, but most authorities caution against the therapeutic use of this agent.

Thus, enterococci are well equipped for survival on hospital wards, and their emergence as important nosocomial pathogens in increasingly susceptible patient populations was predictable. Enterococci rank among the top three pathogens reported to the National Nosocomial Infections Surveillance (NNIS) System. In the most recent NNIS System report,[9] enterococci were recovered from 16% of urinary tract infections, 13% of surgical site infections, and 8% of bloodstream infections (but only 2% of pneumonias). The primary bloodstream infection rate increased significantly during 1980 through 1989, with increases occurring in hospitals of all sizes and in both teaching and nonteaching institutions.[10] These are not trivial infections. Mortality associated with enterococcal bacteremia has been comparable to that observed with other opportunists, ranging from 34% to 46% in some studies. Although it is tempting to blame this high mortality rate on the serious underlying diseases of infected patients, Wenzel's group has demonstrated an attributable mortality of 31% for bacteremic patients."

Because enterococci are intrinsically resistant to so many antibiotics and are killed reliably by none, therapy of enterococcal infections always has been challenging. Synergistic combinations of a β-lactam or glycopeptide and an aminoglycoside generally have been required to cure serious infections outside of the urinary tract. Recent dramatic increases in antibiotic resistance among nosocomial strains of enterococci have complicated therapy considerably and threaten to plunge us into what Mitchell Cohen in a recent paper in Science called a "postantibiotic era"[12] in which patients will die because their bacterial infections are refractory to treatment by all known antimicrobial agents. In the case of the enterococcus, such antibiotic-resistant strains already have arrived.

The first clue that there were therapeutic prob lems lying ahead came in 1970, when enterococci with high-level resistance to streptomycin were detected, precluding synergistic therapy with penicillin. Plasmid-mediated, high-level resistance to gentamicin and other aminoglycosides was noted in Europe in 1979 and in the United States in 1983, essentially depriving clinicians of synergistic bactericidal antibiotic regimens for serious enterococcal infections. Aminoglycoside-resistant strains are now entrenched firmly in many hospitals throughout the world. In one Veterans Affairs hospital, an astonishing 55% of clinical enterococcal isolates were found to be resistant to aminoglycosides, and transmission of this strain within the hospital and to a neighboring institution was demonstrated by plasmid typing.[13] Patients who had been transferred to a long-term care facility were found to serve as a reservoir for repeated introductions of resistant enterococci into the acute care hospital,[14] as has been the case with methicillin-resistant *Staphylococcus aureus* (MRSA) and other nosocomial pathogens that chronically colonize hospitalized patients.

In 1983, the β-lactam arm of synergistic anti-enterococcal regimens came under attack when strains capable of producing β-lactamase began to appear. Like the major genetic determinant for high-level aminoglycoside resistance, the enterococcal β-lactamase gene apparently originated in *S aureus*.[15] In most enterococcal strains, the β-lactamase gene resides on a conjugative plasmid that also encodes high-level aminoglycoside resistance, while in other strains the gene is located in the chromosome and can be transferred by a transposable element. Genotyping by pulsed field gel electrophoresis has demonstrated clonal dissemination of β-lactamase-producing *E faecalis* strains to six hospitals in five states, although strains in other hospitals have different genotypes.[16] Following a period in which only a few sporadic isolates were noted, extensive nosocomial epidemics of β-lactamase-producing, aminoglycoside-resistant strains have begun to appear.[5,17]

Meanwhile, *E faecium,* which always has been relatively more resistant to penicillins than *E faecalis,* has developed high-level resistance to these agents.[18-20] This high-level resistance is not due to production of β-lactamase, but appears to be caused by alterations in penicillin-binding proteins. Thus,

unlike β-lactamase-mediated penicillin resistance, penicillin resistance in *E faecium* cannot be overcome by p-lactamase inhibitors.

And now we are faced with glycopeptide-resistant enterococci.[21] First detected in 1986, strains highly resistant to vancomycin and teichoplanin have spread with alarming speed. In 1989, only 0.8% of enterococcal strains isolated in NNIS Systems hospital intensive care units were resistant to vancomycin; by 1992, 10% of strains were resistant.[22] Outbreaks appear to be occurring frequently The cluster reported by Rubin et al in this issue of *Infection Control and Hospital Epidemiology*[23] joins two other published reports from U.S. hospitals in recent months.[3,6]

Although the mechanism of vancomycin resistance still is being investigated, the critical element appears to be production of 39 Kdal D-alanine:D-alanine ligase with altered substrate specificity resulting in a modified peptidoglycan structure that is not recognized by vancomycin.[24] The *van*A gene responsible for production of this protein is located on a plasmid that can be transferred by conjugation to other enterococcal strains, ***Streptococcus*** *sanguis,* and *Listeria* ***monocytogenes.*** While one group claims to have transferred vancomycin resistance to *S aureus,*[25] others have failed to confirm this alarming report. Enterococcal strains with lower levels of vancomycin resistance also have been reported, but the extent to which they have spread in hospitals is unclear because they are relatively difficult to detect by routine suscep tibility testing methods.

The outbreaks of vancomycin-resistant enterococci published to date have been controlled rather easily by strict application of barrier precautions. However, there is little reason to celebrate, given the demonstrated inability of most hospitals to cleanse themselves of aminoglycoside- and ampicillin-resistant enterococci. So what can beleaguered hospital epidemiologists do to stem the tide, now that multiply resistant enterococci have joined MRSA and gram-negative bacilli resistant to aminoglycosides and advanced-generation β-lactams on the growing "most wanted" list of nosocomial bacteria?

The first step should be to discourage clinicians from using vancomycin promiscuously. This cannot be a quixotic crusade to reduce vancomycin use radically, since this agent has become indispensible in an era of widespread methicillin resistance in staphylococci. However, as suggested by Rubin et al,[23] it is prudent to limit the empiric use of vancomycin in populations such as neutropenic oncology patients, reserving this drug for documented infections. Certainly, prophylactic use should be scrutinized critically. Recently, I was surprised to find that some oncologists in my hospital were promoting routine instillation of vancomycin into central venous lines to prevent catheter-associated coagulase-negative staphylococcal infections, apparently based on a small study in the oncology literature.[26] Equally disconcerting was a study advocating vancomycin prophylaxis for coagulase-negative staphylococcal bacteremia in very low birthweight neonates.[27] Vancomycin prophylaxis in patients receiving prosthetic heart valves and other implanted medical devices may be harder to resist in institutions experiencing high rates of postoperative MRSA and methicillin-sensitive *S aureus* infections.

Because even the most aggressive efforts to restrict the use of antibiotics are unlikely to stop the emergence of antibiotic-resistant nosocomial pathogens entirely, emphasis must be placed on early detection and containment. Once antibiotic-resistant bacteria have disseminated beyond a geographically isolated group of patients, eradication becomes difficult, expensive, and time consuming-if not impossible. Traditional bedside nosocomial infection surveillance cannot provide an adequate early warning system. The problem, of course, is that patients with clinically apparent infections represent only the tip of the iceberg. Indeed, antibiotic-resistant pathogens may spread well beyond an easily containable focus before the first infections appear.

Accordingly, detection efforts must be centered in the clinical microbiology laboratory. In the case of enterococci, laboratories should already be screening routinely for high-level aminoglycoside resistance, high-level penicillin resistance and p-lactamase production, and vancomycin resistance. Strong consideration should be given to performing routine surveillance cultures in high-risk patients, such as those in intensive care units, concentrating on antibiotic-resistant pathogens that have been found sporadically in the institution already but have not yet become widespread and endemic. This can be performed cheaply and efficiently by using selective media containing the appropriate antibiotics. Screening cultures should be tailored to the known ecological preferences of specific microorganisms. For example, stool cultures would be the most costeffective approach to detecting patients colonized with antibiotic-resistant enterococci.

Rapid detection must be accompanied by speedy deployment of effective containment and control measures. Prompt initiation of an effective strategic plan requires an alert, well-trained, interdisciplinary "strike force," including individuals with expertise in infection control, epidemiology, and microbiology. Liberal use of screening cultures, preferably coupled with computerized tracking of colonized patients, should provide a microbiologic and electronic "fence," greatly facilitating containment efforts.


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Resistant bacteria complicate recovery in organ recipients

FIGURE. Headline from an *Atlanta Journal/Atlanta Constitution* article on enterococci with high-level resistance to vancomycin, penicillin, and gentamicin isolated from patients at an organ transplantation center, September 19, 1992.

As hospital epidemiologists prepare for combat on the microbial front, they must also gird themselves for an equally important struggle with hospital administrators. On the one hand, administrators are faced with escalating demands by third-party payors and regulatory and accrediting agencies for clinical outcome data, including nosocomial infection rates. Some of these data, such as surgical site infection rates stratified by underlyiig illness severity, may prove useful eventually for interhospital comparisons. Others, such as the hospital-wide nosocomial infection rates collected by the popular Maryland Hospital Associations occur rence screen system, are virtually useless. All require extremely labor-intensive surveillance. Infection control personnel who are burdened by routine hospital-wide surveillance will find it difficult to sustain a creative, responsive antibiotic resistance detection, containment, and eradication program. Hospital epidemiologists must be strong advocates of nimble, flexible infection control programs.

On the other hand, hospital administrators are under intense pressure to reduce spiralling health care costs. Clinical laboratories are prime targets of professional cost trimmers and efficiency experts because it is widely perceived that diagnostic tests are ordered excessively and inappropriately. While recognizing the importance of reducing unnecessary testing, hospital epidemiologists must help defend the availability and quality of microbiology laboratory services. Screening cultures obtained for epidemiologic purposes generate no revenue, but they are essential components in the battle to contain antibiotic-resistant microorganisms. Sending microbiologists and technologists to national scientific meetings and continuing education courses may be criticized as a luxury, but laboratories that do not perform state-of-the art susceptibility testing will be ill prepared to recognize the arrival of novel antibiotic resistance genes in the institution. Administrators must be convinced that failure to detect resistant bacteria while they still can be contained leads inexorably to expensive, time-consuming epidemic control efforts, prolonged, costly hospital stays for difficult-to-treat nosocomial infections, increased use of expensive advanced-generation antibiotics, and a potential public relations nightmare when antibiotic resistance becomes "headline news" (Figure).

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