Vancomycin-Resistant Enterococci Outside the Health-Care Setting: Prevalence, Sources, and Public Health Implications

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Although nosocomial acquisition and subsequent colonization of vancomycin-resistant enterococci (VRE), an emerging international threat to public health, has been emphasized in the United States, colonization among nonhospitalized persons has been infrequently documented. In contrast, in Europe, colonization appears to occur frequently in persons outside the health-care setting. An important factor associated with VRE in the community in Europe has been avoparcin, a glycopeptide antimicrobial drug used for years in many European nations at subtherapeutic doses as a growth promoter in food-producing animals. In Europe, evidence suggests that foodborne VRE may cause human colonization. Although avoparcin has never been approved for use in the United States, undetected community VRE transmission may be occurring at low levels. Further studies of community transmission of VRE in the United States are urgently needed. If transmission with VRE from unrecognized community sources can be identified and controlled, increased incidence of colonization and infection among hospitalized patients may be prevented.

Vancomycin-resistant enterococci (VRE), first reported in Europe in 1988, are emerging as a global threat to public health (1). The incidence of VRE infection and colonization among hospitalized patients has increased rapidly in the last 7 years. From 1989, the year VRE was first identified in the United States, through 1993, the proportion of enterococcal isolates resistant to vancomycin reported to the National Nosocomial Infections Surveillance System increased 20-fold (2). Infection with VRE may be associated with increased mortality (3,4), and no effective antimicrobial therapy is available for many VRE (5,6).

Multiple factors predispose a person to infection with VRE, but colonization precedes most infections (7). In the United States, nosocomial transmission of VRE from patient to patient has been emphasized (3,7-10). Although VRE introduced into hospitals by colonized patients from VRE-endemic settings has been reported (8,9), it is unclear how VRE is first introduced into most U.S. hospitals.

Although no data so far support significant acquisition and transmission of VRE outside the health-care setting in the United States, a growing number of reports from Europe suggest that colonization with VRE frequently occurs in the community (11-15). Reports from Europe also have suggested that VRE exist elsewhere in the environment, including animal feces and human foods of animal origin (15-23). Additional evidence supports the transmission of VRE to persons in contact with these sources, resulting in an increased human reservoir of VRE colonization (15,16,22). If VRE is frequently introduced into health-care settings from community sources, its control will require community-based initiatives, unlike measures used to control nosocomial pathogens.

This review summarizes the existing evidence for community acquisition and transmission of VRE outside the health-care setting in Europe, relates these findings to the epidemiology

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of VRE in the United States, discusses steps to stem community transmission of VRE, and identifies research needs.

Animal and Community Reservoirs of VRE in Europe

VRE were first reported outside the health-care setting in 1993 when vancomycin-resistant *Enterococcus faecium* was recovered from waste water samples collected from sewage treatment plants in urban areas of England (16) and in small towns in Germany (17). The following year, Bates et al. recovered VRE from livestock feces and from uncooked chicken samples purchased from retail outlets (18). Klare et al. also have found VRE in manure samples from pig and poultry farms in Germany and suggested a possible relationship between the recovery of these organisms and the use of avoparcin, a glycopeptide antimicrobial drug used as a livestock feed additive in many European countries (19). The association between the recovery of VRE from food animals, especially poultry, and the use of avoparcin at subtherapeutic doses for growth promotion has now been confirmed by epidemiologic studies in Denmark (20,21), Norway (22), and the Netherlands (15).

The link between VRE colonization of animals used in food production and human VRE colonization was first suggested by Bates et al., who recovered VRE with identical ribotypes from retail chicken carcasses and humans (17). VRE has also been recovered from poultry and pork collected from slaughterhouses and retail outlets in Germany (19,23), Norway (22), and the Netherlands (15). More recently, a higher prevalence of VRE colonization was found among persons who worked on turkey farms or in turkey processing plants than among urban residents in the Netherlands (15). Because of the heterogeneity of pulsed-field gel electrophoresis patterns encountered in each population and the contrasting similarity of patterns found between individual turkey farmer/slaughterer isolates and animal isolates, the investigators concluded that "dissemination of VRE from animal origin via the food chain seems likely" (15).

The presence of the *vanA*, *vanX*, and *vanR* genes in VRE isolates examined from the feces of pigs and poultry in Denmark (21) suggests that a gene cluster similar to that found on Tn*1546*, the transposon responsible for high-level vancomycin resistance in human isolates (24,25), is responsible for resistance among these animal isolates. Regardless of whether individual clones of VRE are transmitted through the food chain or whether transfer of a transposable genetic element (i.e., Tn*1546*) from VRE-colonized animals to humans occurs, evidence points to a similarity between organisms present in these two populations and suggests transmission of vancomycin resistance between the microbial flora of human and animal species.

If VRE from poultry, swine, and other food-producing animals play a role in human colonization and infection, a significant level of VRE colonization may be found among persons not associated with the health-care setting. In Europe, VRE have been detected among persons outside the health-care setting in several studies (11-14). VRE were isolated from the stool of three (2%) of 184 persons in Oxford, England (11), 7 (17%) of 40 persons living in Charleroi, Belgium, without recent exposure to a health-care setting (12), and 22 (3.5%) of 636 patients cultured within 2 days of entering a hospital in Belgium (13). A community survey in the Netherlands performed on 200 outpatient stool samples submitted from patients with symptoms of diarrhea demonstrated a prevalence of VRE colonization of 2%, a rate similar to the 1%-3% prevalence among hospital inpatients (14). In another survey, 13 (11%) of 117 urban residents in the Netherlands harbored VRE (15).

VRE Outside the Health-Care Setting in the United States

Human VRE colonization outside the health-care setting has not been demonstrated in the United States. No VRE was found in two community prevalence surveys designed specifically to detect VRE (26,27). The number of persons studied, however, remains small (304), and the culture methods used may not have been the most sensitive for detecting small numbers of organisms (26,28).

Other lines of epidemiologic evidence in the United States support the possible existence of community VRE transmission. Although several hospital outbreaks of VRE caused by a limited number of genetic clones have been reported (9,26), polyclonal outbreaks have been observed in other instances (3,10,29,30). Delayed detection of VRE in the hospital population or the presence of a highly mobile element such as Tn*1546* transmitting vancomycin resistance between genetically

dissimilar enterococci could explain this finding. Another plausible but unproven explanation is that a larger community reservoir containing genetically diverse VRE exists. Additional evidence is provided by reports of VRE among patients in medically isolated communities (i.e., isolated population centers served by few inpatient health-care facilities that infrequently receive outside patient transfers) in the United States (L.C. McDonald, unpub. data) and the recent finding of VRE colonization among patients from the community within the first 24 hours of admission to a hospital intensive care unit (31). Finally, the existence of enterococci possessing high-level resistance to aminoglycosides in a community prevalence survey (32) provides evidence that antimicrobial-resistant enterococci can disseminate outside health-care settings in the United States.

If community transmission is occurring in the United States, potential vehicles of such transmission include human or animal food. Antimicrobial resistance in enterococci has been more prevalent in farm animals exposed to antimicrobial drugs (33,34). Although high-level aminoglycoside–resistant enterococci have been recovered from chicken prepared in the cafeteria of a hospital where VRE was endemic (35), isolation of VRE with the VanA phenotype from animals or human foods of animal origin have not been reported. Recovery of VRE with the VanA phenotype from dog food sold in the United States (36) and evidence from Europe suggesting that VRE may be prevalent in household pets (cats and dogs) (37, 38) with a genotype common to both human and pet hosts (37) suggests another mode of community transmission. Finally, transmission of VRE from a recently discharged patient to a family member suggests that household contact, including food preparation, may lead to community transmission in the United States (39).

Implications

If community transmission is important in the global spread of VRE, factors leading to its emergence in this setting must be examined, and measures must be taken to control transmission. In response to data linking the use of avoparcin with the emergence of VRE in the food chain and potential transmission to humans, Denmark (1995) and Germany (1996) imposed bans on the use of avoparcin at subtherapeutic doses in food animals for growth promotion (12,40). This action by two member states has been followed recently by a European Union-wide ban on avoparcin (41). Avoparcin has never been licensed for use in the United States or Canada because of its carcinogenic potential; illegal use, however, has been reported (42).

Feed additive manufacturers have resisted proposals to ban the use of avoparcin at subtherapeutic doses for food animal growth promotion in Europe (43,44). Opponents of the ban have suggested that the relatively low incidence of human VRE infections in European countries where avoparcin has been used for many years, compared with the high rate in the United States, where avoparcin is not used, is inconsistent with the hypothesis that avoparcin is a major factor in the emergence of VRE (43). However, profound differences may exist between the United States and European countries in the amount of glycopeptides used in health-care settings.

Vancomycin use in U.S. hospitals has increased dramatically in the past 10 to 15 years (45,46) because of a variety of factors, including increases in the incidence of methicillin-resistant staphylococci, prosthetic device–related infections, *Clostridium difficile* colitis, and inappropriate use of the drug. Although vancomycin and other glycopeptide use in European health-care settings has not been similarly documented, this marked increase in human glycopeptide use is thought to be primarily a U.S. phenomenon (43). Because the use of vancomycin and other antimicrobial drugs is an important risk factor for human VRE infection (3,7), if glycopeptides were prescribed in European hospitals at levels common in U.S. hospitals, there might be an even greater incidence of VRE infections in Europe. Likewise, given the suspected greater use of glycopeptides in U.S. hospitals, if community carriage of VRE were to increase in the United States, there might be an even greater incidence of VRE infections in U.S. hospitals.

Although the exact role of human antimicrobial use in the transmission of VRE is not known, observations from an animal model (in which mice were orally administered VRE and became only transiently colonized unless simultaneously exposed to antimicrobials [47]) support an important role for antimicrobial drugs in establishing persistent colonization. Antimicrobial drugs used in health-care settings may alter bowel flora, rendering patients more susceptible to colonization by VRE transmitted from other colonized or infected patients. Epidemiologic

evidence of foodborne VRE transmission in the community suggests that antimicrobial drugs may predispose hospitalized patients to colonization with ingested VRE. Contamination of a patient's food may occur during consumption by a variety of mechanisms, including contamination with VRE from the hands of the patient or health-care worker. In areas where VRE is also found in the animal food supply, contamination may also occur during processing by contact with VRE from the bowel flora of the food animal.

In addition to predisposing patients to colonization, some antimicrobial drugs appear to increase the number of enterococci in the stool (48) and may therefore increase the number of VRE in the stool to a level where colonization can become more readily detected by culture methods. Either of these effects could explain the findings of Van der Auwera et al.(49), who described changes in the bowel flora of 22 healthy human volunteers in Belgium who were administered oral glycopeptides (teicoplanin or vancomycin) for 3 weeks in 1989. None had VRE recovered from their stool before exposure to the oral glycopeptide; whereas after such exposure, VRE was recovered from 64% of the volunteers (49). Although this detection of VRE may have represented new colonization from a contaminated food supply or unidentified occupational risk (e.g., employment in a health-care setting), it appears just as probable that exposure to glycopeptides selectively increased the number of VRE already in the large intestine to a level where colonization became detectable.

Conclusion

Questions remain regarding the human and animal origins of VRE. It is clear, however, that the use of glycopeptides in either animal or human VRE-colonized populations can promote colonization through increased selective pressure and changes in bowel flora. Genetically related VRE isolates have been found in livestock, animal carcasses, foods, outpatients, and hospitalized patients, strongly suggesting, if not proving, that interspecies transmission can occur and may contribute to colonization and infection in humans. The recovery of genetically similar isolates at various links along the food chain suggests that ingestion of the organism is a plausible mode of such interspecies transmission. The additional finding that *E. faecium* (the most common species of VRE) may better tolerate exposure to higher temperatures than *E. faecalis* makes survival in undercooked foods appear more plausible (50). After ingestion, factors such as a high organism load, reduced gastric acidity, or recent antimicrobial exposure could allow the organism to more readily establish persistent colonization in the human large intestine. After a VRE-colonized person is admitted to a health-care facility, additional antimicrobial exposure may enable small numbers of VRE in the large intestine to selectively increase to a point where interpatient transmission is promoted, colonization is more readily detected, and clinical infection is more likely to occur (Figure).

If livestock are an important source of VRE for humans, reducing the number of colonized

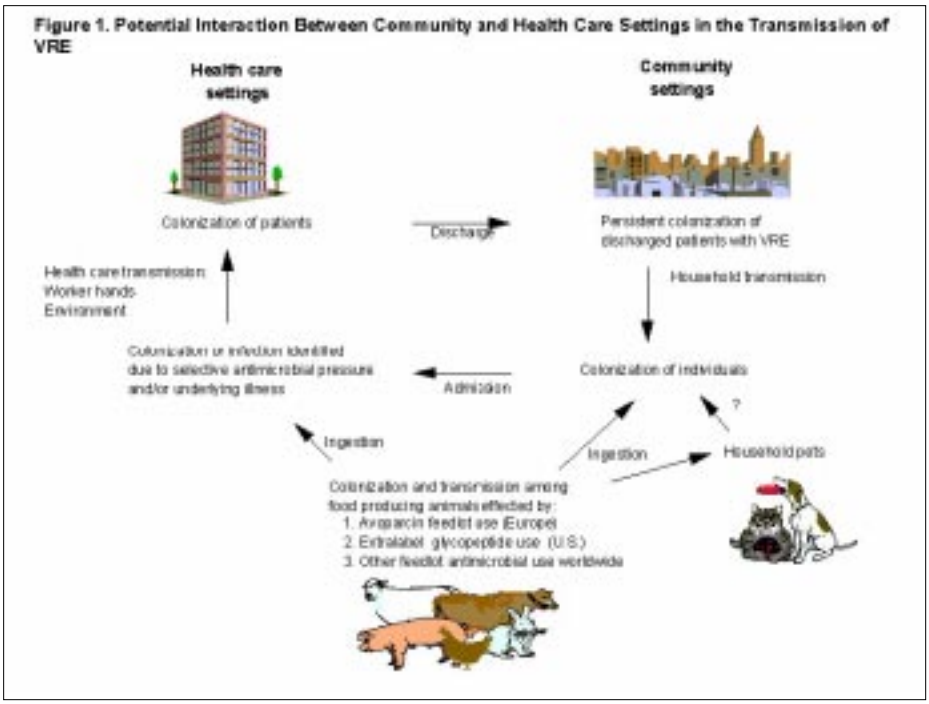

Figure. Potential interaction between community and health-care settings in the transmission of VRE.

livestock would be an effective control measure for limiting VRE infections. Since no therapy exists to eliminate VRE colonization, a rational approach would be to reduce selective pressure for the organism by limiting the use of glycopeptides. Although no glycopeptides are approved for use at subtherapeutic doses in food animals for growth promotion in the United States, vancomycin has been used therapeutically in veterinary medicine. However, a prohibition of extralabel therapeutic use of glycopeptides in food-producing animals has been announced (51). Such a ban would appear a reasonable precautionary measure against transmission of VRE within and between various animal populations and would be consistent with existing control efforts recommended by the Hospital Infection Control Practices Advisory Committee, which emphasizes prudent vancomycin use in humans (52).

The role of community transmission of VRE both within and between animal and human populations in Europe and the United States requires further study. Culture surveys for VRE among healthy human volunteers who have had no recent contact with health-care settings should be performed with sensitive culture methods. Such surveys should include family members of recently discharged patients known to be colonized or infected with VRE. Additional surveys among animal populations used for food production in the United States should also be performed. Finally, additional laboratory investigations using molecular epidemiologic methods will be required to confirm or refute present evidence for transmission of VRE between animal and human populations. If transmission of VRE from unrecognized sources can be identified and controlled, colonization of hospitalized patients may be reduced, leading to lower rates of nosocomial infections due to VRE.

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