Editorial

Vancomycin-Resistant Bacteria

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Gram-positive cocci, in particular coagulase-negative species of staphylococci and enterococci, seem to be the nosocomial pathogens of the 1990s.[1] In the past, vancomycin has been uniformly active against all of these pathogens, although recently some data have brought its clinical efficacy against even susceptible strains of *Staphylococcus aureus* into question.[2] Vancomycin has been used heavily since 1982 for the treatment of infections caused by methicillin-resistant strains of *S* aureus, which are causing a pandemic,[3] and for treatment of infections by gram-positive organisms in patients allergic to the β-lactams. For serious infections with enterococci resistant to p-lactams, either because of penicillin-binding protein (PBP) changes or by production of β-lactamase, vancomycin also has been the most logical choice for therapy.

In the late 1980s, reports of vancomycin-resistance among gram-positives began to appear.[4] We have seen the emergence of a group of intrinsically vancomycin-resistant microorganisms, lactobacilli, pediococci, and leuconostocs as clinically important pathogens.[4] Infections and outbreaks by vancomycin-resistantcoagulase-negativestaphylococci and enterococci also were reported.[4] In the last two or three years, the worldwide dissemination of vancomycin-resistant enterococci has been documented.[4]

Three major phenotypes among vancomycin-resistant enterococci have been described.[5] VanA strains have high-level resistance to vancomycin (minimum inhibitory concentrations [MICs] ≥64 μg/ml) and teicoplanin. The resistance is usually plasmid mediated and transferable to susceptible recipients. The resistance is also usually inducible, but we are aware of unpublished observations of constitutively expressing strains. VanB strains have variable levels of resistance to vancomycin (MICs 162048 kg/ml) but usually remain susceptible to teicoplanin. The resistance appears to be chromosomally mediated and is normally inducible. Constitutive mutants are easily selected by teicoplanin in the laboratory, and such strains are resistant to both teicoplanin and vancomycin at roughly the same level.[6]

VanC strains are only moderately or intermediately resistant to vancomycin (MICs 816 μg/ml), the resistance is intrinsic to certain motile species of enterococci *(Enterococcus gallinarum* and *Enterococcus casseliflavus)*, and they remain susceptible to teicoplanin.[7] These species can cause clinically significant infection. Resistance at levels of ≤64 μg/ml (some VanB and all VanC strains) are difficult for laboratories to detect,[8] and this problem may lead to delays in identification of the problem. Recent changes by the National Committee for Clinical Laboratory Standards in recommendations for vancomycin disk diffusion testing criteria may help ameliorate this problem.

Some antibiotics can be referred to as "last resort" or "end of the line" alternatives because of their remarkable activity against microbes resistant to most other agents. Vancomycin and probably imipenem can be considered members of this group. What are our alternatives when faced with emerging resistance to our last-resort antimicrobials? We can discover and market new antibiotics. We can attempt avoid the resistance by using other agents to which the strains are susceptible, by using efficacious (shown by laboratory testing) combinations, or by using specific inhibitors of the enzyme(s) responsible for resistance. We can endeavor to preserve the activity of the agent by interdicting the dissemination of the

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resistance determinants involved.

An informal survey performed by Dr. George Miller of Schering-Plough (Bloomfield, New Jersey) (Personal communication. 1992) suggests that new structure antibacterials will not be appearing this decade because many companies have decreased or terminated their antibacterial discovery programs, or have maintained only very focused programs. Thus, although in the past, there was always a new antibiotic in our future, this is no longer the case.

We are just now learning enough about the vancomycin resistance mechanism in enterococci to be able to think about specific inhibitors of this system. The article by Karanfil et al[9] emphasizes that resistance to high levels of multiple antibiotics is now occurring in clinical infections such that effective agents for therapy are lacking. In this situation, what are the alternatives for clinicians and their patients? In vitro work[6,10] has suggested that combinations of vancomycin plus penicillin, or the triple combination including gentamicin might be active against vancomycin- and penicillin-resistant enterococci. This strategy is based on our knowledge of certain aspects of the vancomycin resistance mechanism. However, the frequent association of vancomycin resistance with high-level aminoglycoside resistance, as in the report by Karanfil et al," makes the latter observation of limited clinical utility. Others have had success in vitro with combinations including quinolones,[11] although the mechanism by which this combination might work is not yet understood. The quinolone synergy seems to work even in quinolone- and vancomycin-resistant strains. Whether this will work in animals or patients is not yet clear.

Our final alternative is to prevent the dissemination of resistance to preserve the antibiotics we have now until new agents become available in the (distant) future. There are two aspects to prevention of dissemination of resistance. We can try to directly prevent transfer of the resistance determinant between bacteria and we can prevent the transfer of resistant bacteria between patients. We need a great deal more research before we have specific approaches to the former problem. However, Karanfil and co-workers demonstrate once again that the latter goal can be accomplished through good infection control. Microbiological and chart surveillance identified the problem. The institution of control measures that are not beyond the reach of hospitals where the problem is limited frequently work. Whether this principle can be extrapolated to resistance determinants that are already widely disseminated such as *mec* (responsible for methicillin resistance in staphylococci) is controversial. Therefore, our best strategies, for now, are to fund more research in nosocomial infections and antimicrobial resistance and to prospectively survey for vancomycin resistance among enterococci and staphylococci and contain these strains as much as possible to prevent this resistance from reaching pandemic proportions.

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