ORIGINAL CONTRIBUTION

Vancomycin-Resistant Enterococci and Vancomycin-Resistant *Staphylococcus aureus*: Heralding the end of the antibiotic era?

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The emergence of organisms resistant to commonly utilized antimicrobial agents has reached global epidemic proportions. In particular, nosocomial pathogens with antimicrobial resistant pheno types, are presenting significant clinical difficulties. These difficulties arise due to limited efficacious antimicrobial agents available to treat patients infected with these organisms. Two organisms which currently represent major nosocomial pathogens include enterococci and *Staphylococcus aureus*. Both organisms exhibit antimicrobial resistant phenotypes which currently make clinical management difficult. Vancomycin-resistant enterococci (VRE) is endemic in many major US hospitals and outbreaks of this organism have been documented in Canada. More recently, isolates of vancomycin-resistant *Staphylococcus aureus* (VRSA) have been identified in Japan and the US. Vancomycin is often the last line antimicrobial available for treatment of infections caused by these organisms which have acquired resistance to virtually all other antimicrobials used. Therefore, infection control policies must be strengthened to contain the spread of these organisms. As well, these infection control policies must be utilized in conjunction with specific guidelines concerning antimicrobial usage to prevent the selection of new resistant organisms.

INTRODUCTION

The discovery and subsequent development of antimicrobial agents in the 1940s and 50s revolutionized medical care worldwide. For the first time, fatal infectious diseases such as tuberculosis and pneumonia could be treated effectively and countless lives were saved. However, the dawn of the antibiotic era was quickly accompanied by the emergence of microbes with resistant phenotypes to each of the antimicrobials used. Historically, combating antibiotic resistance was simple; use a different antimicrobial. The large number and variety of antimicrobial agents developed by pharmaceutical industry in the past 30 years overshadowed the potential impact of antibiotic resistance and resulted in a sense of complacency by clinicians and scientists. Increasingly however, the spread of antibiotic resistance is posing a significant obstacle to the successful treatment of infectious diseases worldwide.

Currently, resistance has been reported to nearly all classes of antimicrobials known. Furthermore, all the major bacterial pathogens have been shown to have antibiotic resistant variants and pathogens such as *Mycobacterium tuberculosis*, previously thought to be effectively controlled, are making successful comebacks (1). Intensive investigation into the basis for new resistant phenotypes has shown that bacteria have the ability to modify existing or acquire new genetic elements. The latter encode proteins which function to nullify the effects of the various antimicrobial agents. Antimicrobial agents are classed by mechanism of action such as inhibition of cell wall synthesis, inhibition of cytoplasmic membrane synthesis, inhibition of nucleic acid synthesis, inhibition of protein synthesis and modification of energy metabolism (2). Remarkably, clinical bacterial isolates have exhibited resistant phenotypes to each of these classes by a variety of mechanisms including new chromosomal mutations, activation of latent genes or the acquisition of new genetic elements from the environment. Equally as

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disturbing as the ability of bacteria to rapidly develop new antibiotic resistance is their ability to effectively disseminate genetic resistance determinants throughout the bacterial populations. Gene dissemination has been traced throughout bacterial populations by a variety of molecular mechanisms which have demonstrated the role played by chromosomally encoded genes, extrachromosomal elements called plasmids, segments of DNA called transposons, and bacterial viruses in the spread of antibiotic resistance (3).

Both *Staphylococcus aureus* and *Enterococcus* species have acquired multiresistance to antimicrobials. These common pathogens are becoming increasingly more difficult to treat as they accumulate new antimicrobial resistance determinants (4,5).

VANCOMYCIN-RESISTANT ENTEROCOCCI

Enterococci are gram-positive, facultative anaerobic organisms which grow as singles, pairs or short chains (6). As human commensal organisms, the enterococci are well adapted to survival within the gastrointestinal tract. They are also found in a variety of niches including soil, food, water and living animals where they often represent a significant portion of normal gut flora (7). Although not particularly pathogenic, enterococci are the second most common cause of nosocomial infections in the United States and are responsible for a number of diseases ranging from urinary tract infections to life threatening bacteremia and endocarditis (8,9). Several additional clinical syndromes associated with enterococcal infection include intra-abdominal, biliary tract and indwelling foreign device infections (10,11).

The genus *Enterococcus* consists of at least 19 species of which *Enterococcus faecalis* and *Enterococcus faecium* represent the most clinically relevant organisms. *E. faecalis* is observed in approximately 80-90% of clinical isolates, while *E. faecium* accounts for 10-20% (7). These organisms possess virulence factors which facilitate attachment and colonization of host tissues, tissue invasion and immune modulation. Furthermore, the relative ease with which genetic material is horizontally transferred between members of the *Enterococcus* genus and between enterococci and other gram-positive organisms has long been observed (12). The promiscuity of the *Enterococcus* genus coupled with this organism's extremely adept ability to horizontally shuffle genetic material, has facilitated the dissemination of antibiotic resistance traits throughout the genus, resulting in strains of *Enterococcus faecium* that are resistant to every useful antibiotic described (13). Accordingly, the emergence of enterococci as major nosocomial pathogens is due in part to the organism's ability to survive and thrive in the hospital environment where antibiotic usage is high and therefore selection is heavy.

In 1988, the first evidence of a vancomycin-resistant enterococcus (VRE) was reported in Europe by Courvalin *et al.* in the *New England Journal of Medicine* (14). Detailed investigation of multiple subsequent isolates of vancomycin-resistant organisms in the following years resulted in the identification of three distinct antibiotic resistant phenotypes: VanA, VanB and VanC (15). Phenotypic characterisation of vancomycin-resistant enterococci is based on the susceptibility of the organism to both vancomycin and teicoplanin (a yet unlicensed glycopeptide antibiotic in North America). The VanA phenotype is characterised by a high level resistance to both vancomycin and teicoplanin [minimum inhibitory concentration (MIC) >64 mg/L and MIC>16 mg/L, respectively]. Similarly, VanB phenotypic isolates are resistant to vancomycin of varying concentrations (MICs range from 4mg/L to >1000mg/L), but are susceptible to teicoplanin. Both the VanA and VanB phenotypes are inducible in the presence of vancomycin and both phenotypes are transferable by conjugation in certain strains. In contrast to VanA and VanB phenotypes, the enterococcal species *E. gallinarum* and *E. casseliflavus* are intrinsically resistant to low levels of vancomycin (MIC 4-32 mg/L), and susceptible to teicoplanin (15). These species of enterococci represent type VanC, a non-transferable phenotype. As will be discussed, each of the different phenotypic resistance mechanisms are due to the presence of specific genetic elements. Therefore more recent phenotypic classification schemes have been largely supplanted by genotypic mechanisms which function to identify the presence or absence of the specific genes.

Resistance Mechanism

Vancomycin, the prototype glycopeptide antibiotic, was first discovered in the 1950's (17). Unlike β-lactam antibiotics, glycopeptides are inhibitors of cell wall synthesis which do not interact with cell wall biosynthesis enzymes. Rather, these large rigid molecules interact with peptidoglycan precursors at the outer cell membrane surface and thereby disrupt the cross-linking of glycan strands essential for the maintenance of cell wall integrity (18). Vancomycin is active against the majority of gram-positive bacteria. Possibly the most appealing feature of glycopeptides to physicians in the 1980's was the belief that the development of resistance to a class of antibiotics with such a unique mechanism of action would be difficult, if not impossible. Such views were summarised in 1989 by P.E. Reynolds who wrote; "It is also difficult to envisage development of resistance arising from a change in the target site because of the complexity of the peptidoglycan biosynthetic pathway. Changes involving the complete refashioning of peptidoglycan synthesis could not be achieved rapidly, if at all" (18).

Biochemical characterisation of the mechanism of vancomycin resistance demonstrated that in fact enterococci were able to alter peptidoglycan synthesis. In both VanA and VanB clinical isolates, the normal target site for vancomycin binding, the peptidoglycan precursor peptidyl-D-alanyl-D-alanine is altered. In vancomycin-resistant cells the depsipeptide D-alanine-D-lactate, which has significantly reduced affinity for vancomycin, is preferentially synthesized (19). The presence of this novel structure within the bacterial cell wall reduces vancomycin binding and, therefore, confers vancomycin resistance.

Epidemiology and Clinical Management

In comparison with such organisms as *Staphylococcus aureus* or *Streptococcus pneumoniae*, enterococci are con-

sidered weakly virulent. However, the impact of this organism is significantly heightened by the acquisition of antimicrobial resistance including vancomycin resistance, as there are often no effective therapeutic agents commercially available for patients infected with VRE. The lack of efficacious therapeutic options for treatment of VRE, coupled with a growing number of world-wide nosocomial outbreaks of this organism (21-23), has resulted in severe medical and economic problems associated with control and eradication of this bacterium.

Clusters of vancomycin resistant enterococcal infections were observed as early as 1988, and since then have been found with increasing frequency. Initially it was believed that enterococcal isolates causing infection originated endogenously. However, study of enterococcal isolates from outbreak situations by molecular typing mechanisms have demonstrated clonal dissemination of particular organisms throughout hospital wards (23,24). Between April and December 1993 an outbreak of vancomycin-resistant *Enterococcus faecium* occurred in an adult oncology unit in a community teaching hospital located on the east coast of the United States (23). VRE had not been previously identified as a cause of blood stream infection in this hospital. In the 9 month surveillance, 11 patients developed VRE bacteremia. Eight (73%) of the patients died on median post-infection day 8.5. Four deaths were directly attributable to VRE infection.

Outbreaks such as these have led to the introduction of infection control measures such as VRE screening in stool, isolation of colonized and infected individuals, educational programs and restrictions on the unnecessary use of vancomycin (25). Surveillance screening during outbreaks have isolated glycopeptide-resistant enterococci from the hands of health care workers, medication dispensers, pulse oximeters, electronic thermometers and stethoscopes (24,26), prompting the critical evaluation and revamping of infection control procedures.

Characterization of the patients involved in outbreak situations has identified several predisposing risk factors to VRE colonization. These include, severe underlying disease, hospitalisation for an extended period and prior multiple antibiotic treatments, particularly vancomycin medication (23). Outbreaks have been observed primarily within immunocompromised oncology and tissue transplantation patients where, despite the "second rate" pathogenicity exhibited by enterococci, they have caused severe life-threatening disease (21).

Currently, the spread of multidrug-resistant enterococci is presenting a challenge to physicians as treatment for these infections is limited to combined therapy utilizing a β-lactam antibiotic in conjunction with an aminoglycoside (15). However, wide spread resistance patterns to these antibiotics have forced clinicians to turn to experimental antimicrobial agents and combinations whose effectiveness have not yet been proven.

Of particular interest to clinicians and scientists worldwide is the possibility of the transfer of vancomycin resistance from enterococci to other gram-positive organisms as there appears to be no barrier preventing genetic exchange and expression of resistance determinants in such organisms as *S. aureus*, *Streptococcus* species and *Listeria monocytogenes* (27). The fear that the transfer of vancomycin resistance to a "first rate" pathogen such as *S. aureus* has only been heightened by the identification of a strain of *Streptococcus bovis* harboring a vanB related gene (28), and the demonstration of *in vitro* and *in vivo* transfer of glycopeptide resistance from *E. faecalis* to *S. aureus* under laboratory conditions (29).

VANCOMYCIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Staphylococcus aureus is a non-spore forming gram-positive ubiquitous bacterium which causes a wide spectrum of infections in both adults and children (30). *S. aureus* is isolated frequently as the causative agent of skin diseases such as impetigo, bullous impetigo and skin abscesses including furuncles, carbuncles and cellulitus (31). A variety of clinical syndromes are also associated with genetically encoded toxins which are released upon infection. Toxin mediated diseases include staphylococcal food poisoning, scalded skin syndrome and toxic shock syndrome. Finally, invasive disease associated with *S. aureus* bacteremia can be extremely serious and can be associated with the development of endocarditis, osteomyeletis or septic arthritis (32). *S. aureus* is one of the most frequently isolated nosocomial pathogens and in particular, this organism is an important cause of surgical wound infections (31).

Fatality estimates from *S. aureus* infection were as high as 90% in the pre-antibiotic era. Outcomes of *S. aureus* infection were dramatically improved with the introduction of penicillin G in the early 1940s. Shortly after the appearance of penicillin G, select clinical *S. aureus* isolates were observed with penicillin resistant phenotypes (33). The resistance phenotype was found to be due to a penicillinase, an enzyme responsible for the hydrolytic cleavage and thus inactivation of penicillin (34). The development of semisynthetic penicillin derivatives (e.g. methicillin) which were resistant to the hydrolytic action of penicillinases provided a temporary solution. The emergence of multi-drug resistant *Staphylococcus aureus* in the early 1980s severely limited treatment options for patients infected with this bacterium (35). Vancomycin has not only been the drug of choice, but in many cases the sole antimicrobial agent available for the treatment of methicillin-resistant *S. aureus* (MRSA). The appearance of vancomycin-resistant *Staphylococcus aureus* has been anticipated for a number of years. After 30 years of vancomycin use, resistance has emerged in clinical isolates of coagulase negative staphylococcus, and more recently several MRSA strains isolated from patients in the United States and Japan have also been vancomycin resistant (36,37).

In May 1996 in Japan, a 4 month old infant who had undergone heart surgery for pulmonary atresia developed postoperative fever (37). The surgical incision site developed purulent discharge yielding MRSA. Treatment was commenced with vancomycin for 29 days, but fever and discharge of pus continued. Only when the treatment regimen was changed to

a combination of vancomycin and arbekacin (an aminoglycoside recommended for treatment of MRSA) did the purulent discharge subside and the wound begin to heal. Twelve days later the surgical site appeared inflamed and developed a subcutaneous abscess accompanied by a sudden onset of fever. Therapy was resumed with the combination of arbekacin and ampicillin/sulbactam. After six days, the patient's fever subsided. The MRSA strain which was isolated from the purulent discharge at the sternal incision site and from the debridement sample was found to be vancomycin-resistant (MIC: 8 mg/L).

Resistance Mechanisms

The exact mechanism of the intermediate resistance phenotype exhibited by several MRSA strains has yet to be elucidated. Laboratory experimentation has demonstrated the possibility of the transfer of vancomycin resistance from enterococci to other gram positive organisms as there appears to be no barrier preventing genetic exchange and expression of resistance determinants in *S. aureus*. However, PCR analysis of the vancomycin-resistant MRSA strains demonstrated that they did not carry either *vanA* or *vanB* genes (36). Rather it appears that alterations in the cell wall integrity of the organism may play a role in resistance. Electron microscopy indicates that the cell wall is twice as thick as the walls of control strains. There was also a three-fold increase in the production of both penicillin-binding protein PBP2 and PBP2' as measured by Western blotting, and finally a three-fold increase in the production of cell wall murein precursors compared with vancomycin-susceptible MRSA strains (36).

Epidemiology and Clinical Management

The most common method of spread of *S. aureus* is directly from person to person, often on the hands of hospital staff (38). However, other modes of transport, i.e. aerosolization, can occur. As the second leading cause of nosocomial infections and hospital deaths worldwide, it is not surprising that clinical infections are most common in patients in intensive care units and in other high risk wards. Colonization frequently occurs in elderly patients in long-term facilities or in patients with prolonged hospital stays, with previous antimicrobial treatment or in those with surgical wounds and lesions such as pressure sores and burns (39). Although MRSA has not been shown to be more virulent than its methicillin-susceptible counterpart, its spread within hospitals worldwide has been rapid, undoubtedly influenced by widespread antibiotic pressure. The first strains of MRSA were reported in the United Kingdom in 1961 soon after the introduction of methicillin. The first outbreak in the U.S. was reported in 1968 (40) and major interhospital spread has occurred since then. Unfortunately, it is not unrealistic to believe that the spread of vancomycin-resistant *S. aureus*, under the influence of vancomycin use, would undertake similar if not more rapid dissemination dynamics. Equally as disturbing has been the fact that rapid increases in *S. aureus* resistance rates have been documented in institutions utilizing non-β-lactam antimicrobials as front line agents. Resistance to extensively utilized fluoroquinolones (e.g. ciprofloxacin) has increased exponentially in a few short years, attributable to substantial increases in the usage of these agents (41). As vancomycin usage increases, selective pressure will only increase the appearance and dissemination of more VRSA isolates. Fortunately, the isolates of VRSA which have been isolated thus far have been susceptible to antimicrobial agents other than vancomycin or methicillin. Although treatment to date has been successful, the ability of these bacteria to horizontally shuffle genetic resistant determinants suggests the likelihood that a time may come when no antimicrobials will be effective against this organism.

CONTROL OF NOSOCOMIAL SPREAD OF VRE AND VRSA

Various programs have addressed the increasing problem of antimicrobial resistance. Controlling the spread of vancomycin resistance has been the goal of the Hospital Infection Control Practices Advisory Committee (HICPAC) who have worked in collaboration with the Centers for Disease Control and Prevention (CDC) to formulate recommendations for preventing the spread of these resistant phenotypes. HICPAC listed four elements which must be addressed by hospital departments to achieve the prevention and control of vancomycin resistance (25). Firstly, to avoid colonization with VRE, the prudent use of vancomycin by clinicians is crucial. Secondly, hospital staff must be educated in the problem and consequence of vancomycin resistance. Thirdly, resistant micro-organisms must be identified and reported promptly. Finally, the appropriate infection control procedures must be implemented to prevent patient to patient spread of infection (25).

The development of resistance is correlated with the level of antimicrobial use. Overuse of antibiotics has therefore increased the number of resistance conferring mutations. The Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Centers for Disease Control and Prevention (CDC), and the American Society for Microbiology (ASM) have drafted guideline programs that address the proper use of antimicrobials agents (25,42,43). In particular, guidelines to improve the prescribing of antimicrobials in the management of pneumonia, urinary tract infection, outpatient upper respiratory tract infections, prophylaxis for opportunistic infections in AIDS patients and intravascular device infections are currently being introduced and monitored.

Surveillance for antimicrobial resistance allows prompt recognition of particular phenotypes and makes control more likely. Many combinations of surveillance and control measures have been developed and adopted with varying success. Molecular epidemiologic analysis of clinical isolates involved in outbreaks have also proved helpful in the investigation and control of outbreaks, and have identified patterns of transmission in specific hospital settings. Finally, strict hand washing procedures by health care workers, contact isolation, and antimicrobial treatment of the carrier state in health care workers and patients have had an impact on the spread of antibiotic resistance bacteria.

CONCLUSION

As antimicrobial resistance continues to increase, worldwide novel strategies must be adopted to stem the flow of untreatable bacterial infections. Currently at the forefront of these approaches is surveillance for antimicrobial resistant bacteria on a local and global scale. Although vancomycin-resistant enterococci are endemic within numerous U.S. hospitals, only limited outbreaks have been observed in Canada. In conjunction with surveillance, infection control policies to reduce the risk of nosocomial transmission of VRE and the reduction of antimicrobial use to decrease the selection of antibiotic resistance clones have impacted upon the transmission of this organism in Canada. Although it is yet unclear whether vancomycin-resistance in staphylococci is prevalent worldwide, lessons learned from dealing with VRE will impact on strategies to control such an eventuality. In the short term, non-essential vancomycin usage should stop. Laboratories should screen *S. aureus* strains isolated from patients on vancomycin therapy and patients from whom vancomycin-resistant staphylococcus has been isolated should be isolated to prevent spread of the organism.

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REFERENCES

1. Frieden TR,Sherman LF, Maw KL et al. A multi-institutional outbreak of highly drug-resistant tuberculosis. Epidemiology and clinical outcomes. *JAMA* 1996; 276(15): 1229-35.
2. Neu H. The crisis in antibiotic resistance. *Science* 1992; 257 (21): 1064-1072.
3. Clewell DB. Movable genetic elements and antibiotic resistance in enterococcus. *Eur J Clin Microbiol Infect Dis* 1990; 9: 90-102.
4. Linden PK, Pasculle AN, Manez R, Kramer DJ, Fung JJ, Pinna AD, Kusne S. Differences in outcomes for patients with bacteremia due to vancomycin-resistant *Enterococcus faecium* or vancomycin-sensitive *E. faecium. Clin Infect Dis* 1996; 22: 663-70.
5. Williams D et al. Arrival of vancomycin resistance in *Staphylcoccus aureus. Antibiotics Chemotherapy* 1997; 7(2): 1.
6. Boseley GS, Facklam RR, Grossman D. Rapid identification of enterococci. *J Clin Microbiol* 1988; 18: 275-1277.
7. Murray BE: Life and times of the *Enterococcus. Clin. Microbiol. Rev* 1990; 3:46-65.
8. Felmingham D, Wilson APR, Quintana AI, Gruneberg RN. *Enterococcus* species in urinary tract infection. *Clin Infect Dis* 1992; 5: 295-301.
9. Emori TG, Gaynes RP. An overview of nosocomial infections including the role of the microbiological laboratory. *Clin Microbiol Rev* 1993; 6: 428-442.
10. Graninger W, Ragette R. Nosocomial bacteremia due to *Enterococcus faecalis* without endocarditis. *Clin Infect Dis* 1992; 15: 49-59.
11. Khardor N, Wong E, Carasco CH, Wallace S, Patt Y, Bodey GP. Infections associated with biliary drainage procedures in patients with cancer. *Rev Infect Dis* 1991; 13: 587-591.
12. Schaberg DR, Zervos MJ. Intergeneric and interspecies gene exchange in gram-positive cocci. *Antimicrob Agents Chemother* 1986; 30: 817-822.
13. Leclerq R. Enterococci aquire new kinds of resistance. *Clinical Infectious Diseases.* 1997; 24: 580-4.
14. Leclerq R, Derlot E, Duval J, Courvalin P. Plasmid mediated resistance to vacomycin and teicoplanin in *Enterococcus faecium. N Engl J Med* 1988; 319: 157-161.
15. Leclerq R, Courvalin P. Resistance to glycopeptides in entero cocci. *Clin Infect Dis* 1997;24: 545-56.
16. Tyrrell GJ, Bethune R, Willey B, Low D. Species identification of enterococci via intergenic ribosomal PCR. *J. Clinical Microbiol* 1997; 35: 1054-1060.
17. McCormick MH, Stark WM, Pittenger GE, Pittenger RC, McGuire JM. Vancomycin. a new antibiotic. *In Chemical and Biologic Properties: Antibiotics Annual.* 1956; pp. 606-611.
18. Reynolds PE. Structure, biochemistry, and mechanism of action glycopeptide antibiotics. *Eur J Clin Microbiol Infect Dis* 1989; 2: 943-950.
19. Evers S, Quintiliani R, Courvalin P. Genetics of glycopeptide re sistance in enterococci. *Microbial Drug Resistance* 1996; 2: 219-223.
20. Schaberg DR, Culver PA, Gaynes RP. Major trends in the microbial etiology of nosocomial infections. *Am J Med* 1991; 313 (Supp.): 3B-72S-3B-75S.
21. Papanicolaou G, Meyers B, Meyers J, Mendelson M, Lou W., Emre S, Sheiner P, Miller C. Nosocomial infections with vancomycin resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996; 23: 760-766.
22. Suppola JP, Volin L, Valtonen V, Vaara M. Overgrowth of *Enterococcus faecium* in the feces of patients with hematologic malignancies. *Clin Infect Dis* 1996; 23: 694-697.
23. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Huang T, Sanford MP, Wenzel RP. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin Infect Dis* 1995; 20: 1126-33.
24. Livornese LL, Dias S, Samel C. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. *Ann Intern Med* 1992; 117: 112-116.
25. Centers for Disease Control and Prevention. Preventing the spread of vancomycin resistance - report from the hospital infection control practices advisory committee. *Federal Register* 1994; 59: 25757-25763.
26. Karafil LV, Murphy M, Josephson A. A cluster of vancomycin resistant *Enterococcus faecium* in an intensive care unit. *Infect Control Hosp Epidemiol* 1992; 13: 195-200.
27. Murray BE. What can we do about vancomycin-resistant enterococci. *Clin Infect Dis* 1995; 20: 1134-1144.
28. Poyart-C, Pierre C, Quesne G, Pron B, Berche P, Trieu-Cuot P. Emergence of vancomycin resistance in the genus Streptococcus: characterization of a vanB transferable determinant in *Streptococcus bovis. Antimicrob Agents Chemother* 1994; 41: 24-29.
29. Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus. FEMS Microbiol Lett* 1992; 93: 195-198.
30. Musher DM, MacKenzie SO. Infections due to *Staphylococcus aureus Medicine* 1977; 56: 383.
31. Boyce JM. Nosocomial staphylococccal infections. *Ann Intern Med* 1981; 95: 241.
32. Iannini PB, Crossley K. Therapy of *Staphylococcus aureus* bacteremia associated with a removable focus of infection. *Ann Intern Med* 1976; 84: 558.
33. Hobby GL, Meyer K, Chaffee E: Activity of penicillin *in vitro Proc Soc Exp Biol Med* 1942; 50: 277.
34. Bondi A, Dietz CC: Penicillin resistant staphylococci. *Prec Soc Exp Biol Med* 1945; 60:55.
35. Panlilio AL, Culver DH, Gaynes RP et al. Methicillin-resistant *Staphylococcus aureas* in US Hospitals, 1975-1991. *Infect. Control Hosp Epidemiol.* 1992;13: 582.
36. Hiranastsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC.

Methicillin-resistant *Staphylococcus aureas* clinical strain with reduced vancomycin susceptibility. *Journal of Antimicrobial Chemotherapy* 1997; 40: 135-146.
37. CDC Update. *Staphlycoccus aureus* with reduced susceptibility to vancomycin - United States , 1997. *MMWR* 1997; 46: 813.
38. Struelens MJ, Merten R. Groupment pour le despitage, l'etude et al prevention des infections hospitalieres: National survey of methicillin-resistant *Staphylococcus aureas* in Belgian hospitals: Detection methods, prevalence trends, and infection control measures. *Eur J Clin Microbiol Infect Dis* 1994; 13:56.
39. Ayliffe GA. The progressive intercontinent spread of methicillin-resistant *Staphylcoccus aureas. Clinical Infectious Diseases* 1997; 24, (sup 1): 574-9.
40. Barrett FF, McGee RF, Finland M. Methicillin-resistant *Staphylcoccus aureus* at Boston City Hospital. Bacteriologic and epidemiologic observations. *N Engl J Med* 1968; 279: 441-8.
41. Sreedharam S, Peterson LR, Fisher LM. Ciprofloxacin resistance in coagulase-positive and negative staphlycocci: Role of mutations at serine d4 in the DNA gyrase A protein of *Staphylococcus aureus* and *Staphylcoccus epidermidis. Antimicrob Agents Chemother* 1991; 35: 2151.
42. American Society for Microbiology (ASM). Report of the ASM task force on antibiotic resistance. *Antimicrob Agents Chemother* 1995; (sup 1).
43. Shales DM, Gerding DN, John JF et al. SHEA/IDSA Joint committee on the prevention of antimicrobial resistance: Guidelines for the prevention of the antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol* (In press).

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Martin MacKinnon is presently entering his third year of study at Dalhousie University's Faculty of Medicine. Previously Martin has been granted the degree of Bachelor of Science and in May 1998 he was conferred with the degree of Master of Science in Microbiology and Immunology. Martin's graduate work focused on the study of vancomycin resistant enterococcus (VRE), specifically the characterization of variant VRE isolates. In the future Martin plans to continue work in broad research areas as he completes his medical education.

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