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Review

Vancomycin-resistant enterococci: Troublemaker of the 21st century

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ABSTRACT

The emergence of multidrug-resistant and vancomycin-resistant enterococci during the last decade has made it difficult to treat nosocomial infections. Although various enterococcal species have been identified, only two (*Enterococcus faecalis* and *Enterococcus faecium*) are responsible for the majority of human infections. Vancomycin is an important therapeutic alternative against multidrug-resistant enterococci but is associated with a poor prognosis. Resistance to vancomycin dramatically reduces the therapeutic options for enterococcal infections. The bacterium develops resistance by modifying the C-terminal D-alanine of peptidoglycan to D-lactate, creating a D-Ala-D-Lac sequence that effectively reduces the affinity of vancomycin for the peptidoglycan by 1000-fold. Moreover, the resistance genes can be transferred from enterococci to *Staphylococcus aureus*, thereby posing a threat to patient safety and also a challenge for treating physicians. Judicious use of vancomycin and broad-spectrum antibiotics must be implemented, but strict infection control measures must also be followed to prevent nosocomial transmission of these organisms. Furthermore, improvements in clinical practice, rotation of antibiotics, herbal drugs, nanoantibiotics and the development of newer antibiotics based on a pharmacogenomic approach may prove helpful to overcome dreadful vancomycin-resistant enterococcal infections.

Contents

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1. Introduction

Enterococci are Gram-positive, facultative, anaerobic bacteria that live as part of the natural flora in the intestinal tract of humans and animals and are considered as bacteria of low pathogenicity that only infect immunocompromised patients in oncology, haematology, nephrology and transplantation units of hospitals [1,2]. Among all of the enterococcal species known to date, *Enterococcus faecalis* and *Enterococcus faecium* are the most important species causing infections in humans [1]. Enterococci have taken the upper hand over the past few decades as frequent causes of multiple-antibiotic-resistant, hospital-acquired bloodstream, urinary tract and surgical wound infections and because of their capacity to transfer antibiotic resistance to other microbes [3]. Vancomycin and teicoplanin are important therapeutic alternatives against penicillin-resistant enterococci and other Gram-positive bacteria [4]. Resistance to glycopeptides dramatically reduces the therapeutic options in enterococcal infections; therefore, this class of acquired antibiotic resistance is of special interest from a medical point of view and is discussed in detail in this review. Moreover, glycopeptide-resistant enterococci were first described in France and the UK but today are found in many parts of the world. In US hospitals in particular, a striking increase in glycopeptide-resistant enterococci has occurred in the last decade [5]. Sensible employment of vancomycin and broad-spectrum antibiotics is recommended, and stringent infection control measures must be implemented to prevent nosocomial transmission of these organisms [6].

The reason for the emergence and spread of vancomycin-resistant enterococci (VRE) during the last two decades is not yet fully understood. This fact, obviously, is also a reason for the increased occurrence of enterococcal resistance altogether in hospital infections in the last 20–30 years [7]. Nevertheless, various hypotheses and proposals regarding VRE are being vigorously and extensively debated. The Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines recommend periodic culture surveys to detect VRE colonisation in hospitals with at-risk patients before VRE have been detected in routine clinical specimens [8]. When VRE are detected in the hospital milieu, intensified screening is recommended to aid the earlier identification of colonised patients.

The first report of clinically relevant vancomycin resistance in enterococci was published 26 years ago by Uttley et al., and in 1989 the in vitro transfer of *vanR* genes from enterococci to streptococci, *Lactococcus lactis* and *Listeria* spp. was described [9,10]. The *vanA* gene, which is frequently plasmid-borne and confers high-level resistance to vancomycin, can be transferred in vitro from enterococci to a variety of Gram-positive micro-organisms, including *Staphylococcus aureus* [11]. In this review, we have tried to highlight the rapid worldwide emergence of VRE as well as its causes, genetic basis and occurrence. Simultaneously, we also discuss the importance of vancomycin as a main antibiotic used against Gram-positive bacterial infections and how antibiotic use and misuse in hospitals contributes to the emergence of VRE. Lastly, we have tried to shed some light on the various future approaches to prevent and control VRE.

2. Why do we care about enterococci?

Enterococci constitute an integral part of the bowel flora of humans and the majority of animals [12]. Enterococci are common inhabitants of the alimentary canal and are the cause of urinary tract infections, bacteraemia and endocarditis. They are also commonly recovered from infections of the abdomen, pelvis, biliary tract and wounds, settings in which polymicrobial flora are common. Less frequently, enterococci cause infections of other sites, e.g. joints and the meninges. *Enterococcus faecalis* causes the majority of enterococcal infections overall. *Enterococcus faecium* causes a substantial proportion of enterococcal infections, particularly infections acquired in the hospital setting. Indeed, *E. faecium* has been classified as one of the key problem bacteria abbreviated as ESKAPE (*E. faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.) by the Infectious Diseases Society of America (IDSA), entailing the requirement of new therapies and treatment strategies [13].

Enterococci are very robust organisms because they are able to grow in 6.5% sodium chloride as well as at a wide range of pH and temperatures (between 10 °C and 45 °C) [14]. They can survive on inanimate objects for weeks, a feature that allows them to adapt well to any environment and contributes to their nosocomial transmission [15,16]. Enterococci also have the ability to tolerate sodium azide and concentrated bile salts, which eradicate or hamper the growth of most micro-organisms. The ability to colonise for long periods, often without ill effects, and to survive on inanimate objects makes them more pathogenic in extreme or difficult conditions [17–20].

3. Vancomycin: the gold standard

Edmund Kornfeld isolated vancomycin from the organism *Amycolatopsis orientalis*. It was initially called compound 05865, before clinical trials began. A switch from picric acid precipitation to passage over an ion-exchange resin was an improvement and the resulting drug was named 'vancomycin' (from the word 'vanquish') and was made available for clinical trials [21]. Vancomycin belongs to the glycopeptide class of antibiotics. Severe infections caused by Gram-positive bacteria are treated with glycopeptide antibiotics (vancomycin) [22]. The original indication for vancomycin was for the treatment of penicillin-resistant *S. aureus*. The primary mode of bactericidal action of vancomycin in Gram-positive organisms involves disruption of peptidoglycan polymerisation by binding to peptides containing D-alanyl-D-alanine, the substrate of peptidoglycan synthetase [23]. Vancomycin is an amphoteric glycopeptide antibiotic that is active against Gram-positive bacteria, including meticillin-resistant staphylococci, penicillin-resistant *Corynebacterium* and *Clostridium difficile* [11,24,25].

4. Mechanisms of vancomycin resistance

The most intriguing question, of course, is from where the resistance genes, especially *vanA* and *vanB*, originate. Resistance to antibiotics such as penicillin and vancomycin was thought to be intrinsic until the discovery of conversion of non-tolerant isolates of *E. faecalis* into tolerant ones by exposure to increasing doses of penicillin [26]. Considering the multicentric nature of the emergence of VRE in Europe and the USA as well as the complexity of the mechanisms of vancomycin resistance, it is unlikely that these genes have accumulated in enterococci owing to selective antibiotic pressure alone. The resistance genes stay dormant until any antibiotic is used in a patient. More likely these genes reach enterococci via horizontal gene transfer, and enterococci exhibit both intrinsic and acquired resistance patterns [27]. Various genes conferring intrinsic resistance reside on the bacterial chromosome and are characteristic to enterococci species and specifically modify the C-terminal D-alanine of peptidoglycan to D-lactate, creating a D-Ala-D-Lac sequence that effectively diminishes the affinity of vancomycin for the peptidoglycan by 1000-fold [28]. At the molecular level, vancomycin-resistant bacteria bring only one change, that is the amide link of the two peptidoglycan alanines is replaced by a ketone group, thereby eliminating one of the