Vancomycin resistant enterococci healthcare associated infections

G.B. Orsi*, V. Ciorba**

Key words: Enterococcus species, Vancomycin resistance, healthcare infections
Parole chiave: Enterococcus species, Vancomicina resistenza, infezioni ospedaliere

Abstract

**Background:** Vancomycin-resistant enterococci (VRE) are among the most common healthcare associated multidrug-resistant organisms. Purpose of the article was to review recent data regarding the epidemiology, clinical issues and infection control of this organisms.

**Methods:** A PubMed-MEDLINE search was carried out.

**Results:** The European Antimicrobial Resistance Surveillance System (EARSS) highlights a large variability between the various european countries, with VRE ranging from <2% (Finland, Holland) to >20% (Ireland, Greece, Portugal). Italy shows a low rate level (4.2%). In USA according to the National Healthcare Safety Network (NHSN) in 2006-2007 overall 33% of enterococci were resistant to vancomycin, whereas in Canada VRE prevalence showed to be much lower <10%. Although with some methodological limits, several studies showed that infections caused by VRE are more serious and associated to a higher mortality rate and economic burden compared to those caused by vancomycin susceptible enterococci (VSE). The average increased associated mortality was over two-fold. Resistance to newer antimicrobial agents as daptomycin and linezolid has been described, complicating treatment options for infections caused by these organisms.

**Conclusion:** Control measures aimed at reducing the incidence of VRE colonization and infection in healthcare settings should include: hand washing with an antiseptic or a waterless antiseptic agent, routine screening for vancomycin resistance among clinical isolates, rectal surveillance cultures, contact isolation for patients with VRE and antimicrobial stewardship.

Introduction

Enterococci are normal components of the human intestinal flora, but may become responsible for serious infections as endocarditis or complicated urinary tract infections, in patients with anatomical alterations (i.e. stenosis or insufficiency of heart valves, urethral stenosis). They are also among the major agents of healthcare infections as bloodstream, intra-abdominal and surgical-site infections.

Enterococcus faecalis and Enterococcus faecium are important healthcare associated pathogens and represent the third to fourth most prevalent nosocomial pathogen worldwide. Acquired resistance, most prominently to penicillin/ampicillin, aminoglycosides (high level resistance) and glycopeptides are reported in an increasing number of isolates determining a limited therapeutic spectrum (1).

Therefore the emergence and spread of resistant enterococci, particularly...
vancomycin resistant enterococci (VRE), represents a major public health problem (2, 3).

**Enterococci multidrug resistance**

All *Enterococcus* species, including those of greatest clinical significance as *Enterococcus faecalis* and *Enterococcus faecium*, are naturally resistant to several antibiotics (cephalosporins, clindamycin, cotrimoxazole, aminoglycosides) (4). During the last three decades, resistance to glycopeptides has progressively emerged as a major clinical issue. Vancomycin had been used since the 1950s, but the emergence of resistance in *Enterococcus* species was not reported until 1988 in the United Kingdom and France. Incremental vancomycin usage for MRSA infection may explain the timing. VRE spread throughout Europe and North America and nowadays 80% rates have been reported for *E. faecium* in some areas (3).

Molecular studies on vancomycin resistant enterococci (VRE) have documented at least six acquired resistance types (*VanA*, *VanB*, *VanD*, *VanE*, *VanG*, and *VanL*) and an additional type that is intrinsic to *E. casseliflavus/flavescens* and *E. gallinarum*. However, only *VanA* and to a lesser extent *VanB*, both in *E. faecium*, are widely prevalent (5). Strains that carry the *vanA* gene typically demonstrate high resistance to vancomycin and teicoplanin, whereas those isolates that carry the *vanB* gene are resistant to vancomycin (but with lower MICs than *vanA* isolates) and susceptible to teicoplanin. However teicoplanin should never be considered as an alternative to vancomycin because strains may acquire resistance in vivo (6). Most VRE cases in Europe and USA are now due to *vanA*, whereas the epidemic in Singapore and Australia has predominantly been *vanB* (2).

Of note, vancomycin resistance genes transfer from enterococci to other organisms is possible, causing the emergence of vancomycin resistant *Staphylococcus aureus* (VRSA) (7).

**Epidemiology**

Most entrococcal infections are due to *E. faecalis* (80%), although epidemiology is changing, and *E. faecium* isolates now account for up to 20% (1, 8). The latter species acquisition of resistance is a major cause of concern, because intrinsically resistant to aminoglycosides (1).

In Europe, surveillance data show a large variability between the various countries with VRE ranging from <2% (Finland, Holland) to >20% (Ireland, Greece, Portugal). Italy is a country with a low rate level (4.2%) (8) (Table 1). In the UK vanA is now seen in 15%-25% of *Enterococcus faecium* and 2% - 3% of *Enterococcus faecalis*, rates it reached in the early 1990' (2, 9).

Rates of vancomycin resistance in USA hospitals reached much higher levels. According to the National Healthcare Safety Network (NHSN) in 2006-2007 (10), overall 33% of enterococci were resistant to vancomycin and other recent estimates confirm the diffusion (11, 12). Differently in Canada VRE prevalence showed to be very lower <10% (13) (Table 1).

VRE epidemiology in USA and Europe seems to be very different. In North America VRE reservoirs are present predominantly in healthcare facilities and in the hospitals outbreaks are frequent. On the opposite in Europe the major reservoir of VRE was initially represented by the healthy population in the community, 2% - 10% of whom were carriers. The source was most likely caused by the use of avoparcin, a vancomycin like glycopeptide adopted in the agricultural industry as a growth promoter for animals during the 1980', explaining the community reservoir (7). Recently, the epidemiology
Table 1 - Most recent studies on vancomycin resistant enterococci prevalences in various parts of the world

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Settings</th>
<th>Patient population</th>
<th>Percentage of isolated pathogens</th>
<th>Vancomycin resistant enterococci</th>
<th>Resistance range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARSS 2011</td>
<td>Europe</td>
<td>900 hospitals, in 28 countries</td>
<td>General hospital population</td>
<td>-</td>
<td>&lt;1% - &gt;30%</td>
<td>Ireland 34.9%, Greece 23.1%, Portugal 20.2%</td>
<td>8</td>
</tr>
<tr>
<td>NHSN 2006-2007*</td>
<td>USA</td>
<td>463 hospitals</td>
<td>88% ICU population</td>
<td>* E. faecalis 3.5%</td>
<td>33%</td>
<td>*VR-E. faecium (80%)</td>
<td>10</td>
</tr>
<tr>
<td>INICC 2003-2008*</td>
<td>Worldwide</td>
<td>173 ICUs, in 25 countries</td>
<td>ICU population</td>
<td>-</td>
<td>* CL-BSI 8.7%</td>
<td>-</td>
<td>44</td>
</tr>
<tr>
<td>Canada 2005-2006</td>
<td>Canada</td>
<td>19 ICUs</td>
<td>ICU population</td>
<td>Enterococcus spp. 6.1%</td>
<td>6.7%</td>
<td>-</td>
<td>13</td>
</tr>
</tbody>
</table>

Legend: CAUTI': CL-BSI: central line associated bloodstream infection; EARSS: European Antimicrobial Resistance Surveillance System
* Pathogens responsible for HAI

Clinical Issues

VRE are a particular problem in the ICUs of large hospitals where they usually cause a variety of infections (e.g., endocarditis, bloodstream, urinary tract,...). Transmission can occur through direct contact (e.g. endocarditis, bloodstream, urinary tract,...) or via contaminated patient-care workers, or via contaminated patient-care equipment or environmental surfaces. Other risk factors for VRE nosocomial transmission are: prolonged hospitalization, use of broad-spectrum antimicrobials, antacids, steroids, severity of underlying diseases, prior surgery, and a low albumin level (16). The duration of colonization may be extremely prolonged ranging between 7 weeks and 3 years (17, 18). Although evidence strongly suggest spread among patients colonized with the bacteria, there is no difference between those colonized or infected. Infection with VRE usually develops in patients colonized with the bacteria. (5) and therefore preventing colonization represents a goal specially in ICU’s (19). Some investigators suggest that VRE bacteraemia may serves more as a marker of severity of illness than as an independent risk factor for mortality (20, 21). Although with some methodological limits, various authors evaluated the excess hospital cost associated with VRE (22), which is changing with reports of hospital outbreaks as previously described in the USA (14, 15).
Two large meta-analysis concluded that mortality rate caused by VRE-BSI is at least double of VSE-BSI. The first (nine studies) concluded that patients with VRE bacteraemia were more likely to die than patients affected by VSE bacteraemia (OR 2.5; CI 1.9-3.4) (27).

In particular two studies considered patients with VRE bloodstream infection (BSI) estimating an extra cost of $27,190 comparing VSE BSI (28) and $86,290 compared to matched control patients without BSI (22).

### Therapy and Management

As enterococci are tolerant to penicillins, their success in killing enterococcal bloodstream infections relies on the synergistic combination of a cell wall active agent (gentamicin or streptomycin) with an aminoglycoside (gentamicin or streptomycin) being lost versus isolates that acquire determinants conferring high-level resistance (HLR) to these antibiotics. HLR to ampicillin/penicillin, caused by modification and/or overproduction of some penicillin binding proteins (PBPs), is very rare in E. faecalis and almost always present in E. faecium. On the other hand, HLR to aminoglycosides is nowadays approaching 30 to 50% in enterococcal infections, and is not infrequently encountered among isolates of enterococcal endocarditis. In this latter circumstance, the combination of ampicillin and amoxicillin or ceftizoxime proved synergistic in vitro studies and in vivo animal models and appeared a promising regimen for treatment of endocarditis in a small series (1, 3, 29).

Therapeutic options against VRE include Table 2. Impact of vancomycin resistant enterococci on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Infection</th>
<th>Controls patient population</th>
<th>Finding</th>
<th>p value</th>
<th>Multivariate analysis OR (95% CI)</th>
<th>p value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective cohort</td>
<td>Teaching hospital</td>
<td>Infection/Colonization</td>
<td>113/113 Not colonized patients</td>
<td>42.5% vs. 28.3%</td>
<td>-</td>
<td>1.6 (1.0-2.6)</td>
<td>&lt;0.04</td>
<td>24</td>
</tr>
<tr>
<td>Case-control</td>
<td>Teaching hospital</td>
<td>Infection/Colonization</td>
<td>53/106 Not colonized patients</td>
<td>24.5% vs. 4.7%</td>
<td>p&lt;0.01</td>
<td>3.1 (0.6-15.1)</td>
<td>0.2</td>
<td>25</td>
</tr>
<tr>
<td>Matched cohort study</td>
<td>Teaching hospital</td>
<td>Infection/Colonization</td>
<td>233/647 Not colonized patients</td>
<td>17% vs. 6%</td>
<td>p&lt;0.04</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Hospitals</td>
<td>Infection/Colonization</td>
<td>9 Studies Vancomycin susceptible enterococci</td>
<td>2.5 (1.9-3.4)</td>
<td>p&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Hospitals</td>
<td>Infection/Colonization</td>
<td>13 Studies Vancomycin susceptible enterococci</td>
<td>45.2% vs. 19%</td>
<td>p&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>22</td>
</tr>
</tbody>
</table>
bacteriostatic agents as linezolid, quinupristidalfosprin (not active against \textit{E. faecalis}), and tigecycline. Daptomycin shows bactericidal activity against enterococci, and may prove useful for serious infections as endocarditis where this aspect is important (30). However its activity may prove borderline at presently recommended dosages, thus high dose regimens should be studied in this setting. Another possible therapeutic approach, that should merit investigation, is adoption of an ampicillin-daptomycin regimen as this combination proved synergistic in vitro against vancomycin-resistant \textit{E. faecium} (7, 31).

As in \textit{S. aureus} and coagulase negative staphylococci, resistance to these newer agents has been already reported usually during protracted therapies. Linezolid resistance, mediated by point mutations in 23S rRNA genes, has been reported in \textit{E. faecium} isolates representing a single clone in two UK hospitals. On the other hand, only anecdotal cases of daptomycin or tigecycline resistance have been reported (1, 3).

**Prevention**

VRE control is considered highly challenging for a number of reasons, the principal is that the reservoir is wide and occult with unsuspected faecal carrier patients being a major reservoir. Generally, for one hospitalized patient with an infection caused by VRE, from 2 to 10 contact patients may are carriers (32).

The first guidelines for VRE control in hospitals were published in 1994 by the CDC Hospital Infection Control Practices Advisory Committee (33), and were followed later by others emphasizing the need for a multifaceted approach (34, 35). All guidelines recommend education of healthcare workers including hand washing with an antiseptic or a waterless antiseptic agent, routine screening for vancomycin resistance among clinical isolates, rectal surveillance cultures, contact isolation for patients with VRE and antimicrobial stewardship.

Transmission control is fundamental for slowing the emergence and spread of antimicrobial resistance, as carefully designed mathematical modelling studies have provided insight into the epidemiologic phenomena governing this observation (36). Transmission control is not only effective in reducing the incidence of infections caused by the targeted pathogens, but actually offers collateral benefit avoiding other multidrug-resistant organisms (MDRO) spread. This phenomenon is largely mediated by the fact that patients colonized with one resistant pathogen are frequently colonized with other MDRO. Relatively high rates of co-colonization by MRSA, VRE and other MDRO have been reported (35, 37, 38). Thus transmission control (e.g. contact precautions, hand hygiene...) acts on multiple antimicrobial-resistant pathogens. Simple measures to prevent the spread of VRE include the use of isolation gowns, gloves and face shields when performing patient care.

The use of active surveillance programs is another evidence-based approach for preventing VRE transmission. VRE screening is carried out on stool specimen or rectal/perirectal specimen, also a rapid real-time PCR test that detects the presence of vanA and/or vanB genes has been proposed for rapid screening to identify patients harbouring VRE at hospital admission (39). Ostrowsky et al (40) with an active infection-control intervention including surveillance cultures and infected patients isolation succeeded in reducing or eliminating VRE in the healthcare facilities of a region.

Following positive screening, patients should be placed in contact precautions and decolonised, although MDRO decolonization is still a matter of debate. As other MDRO, VRE may survive on surfaces and medical
equipment in the hospital environment. Duckro et al. (41) demonstrated that healthcare workers can contaminate their hands with VRE from objects, or from intact patient skin surfaces and transfer these organisms to other surfaces. The authors reported 11% of sites touched by colonized healthcare workers became VRE positive (41). As VRE may present resistance to routine cleaning in the hospital environment, improved environmental cleaning and reduced risk of acquisition of VRE has been shown (42, 43). Due diligence in antimicrobial prescribing patterns also plays an essential role in preventing the development of VRE infections and all types of resistant organisms. Antibiotic use has been identified as one of the most important risk factors for VRE acquisition. In case-control studies, colonization and infection with VRE have been associated with exposure to vancomycin, third generation cephalosporins, ciprofloxacin and aminoglycosides (16).

Conclusions

VRE have become common in many hospitals throughout the world and, once established, show to be very difficult to eradicate. They are also difficult to treat and most severe infections will need a combination therapy because many of the effective antimicrobial agents, when used alone, have only a bacteriostatic effect. Therefore infection control measures are of prime importance in preventing the establishment of these pathogens and controlling the spread.

Control measures aimed at reducing the incidence of VRE colonization and infection in healthcare settings should include: hand washing with an antiseptic or a waterless antiseptic agent, routine screening for vancomycin resistance among clinical isolates, rectal surveillance cultures, contact isolation for patients with VRE and antimicrobial stewardship.

Riassunto

Infezioni correlate all’assistenza da enterococchi vancomicino resistenti

Introduzione: Gli enterococchi vancomicino-resistenti (VRE) sono tra i più comuni microrganismi responsabili di infezioni ospedaliere. Finalità di questo studio è di effettuare una revisione della letteratura recente riguardo l’epidemiologia, gli aspetti clinici ed il controllo delle infezioni causate da questo microrganismo.

Metodi: E’ stata effettuata una ricerca utilizzando la banca dati PubMed-MEDLINE.

Risultati: I dati forniti dallo European Antimicrobial Resistance Surveillance System (EARSS) evidenziano un’ampia variabilità tra i vari paesi europei, con tassi che oscillano da <2% (Finlandia, Olanda) a >20% (Irlanda, Grecia, Portogallo). In Italia è stato registrato un livello basso (4,2%). In generale negli USA, secondo il National Healthcare Safety Network (NHSN), nel 2006-2007 il 33% degli enterococchi sono risultati resistenti alla vancomicina, mentre in Canada la prevalenza di VRE si è dimostrata inferiore (<10%). Nonostante alcuni limiti metodologici, diversi studi hanno evidenziato come le infezioni causate da VRE fossero più gravi, associate ad una mortalità più elevata e ad un costo economico maggiore rispetto a quelle determinate da enterococchi vancomicino sensibili (VSE). L’incremento medio della mortalità associata era superiore al doppio. La resistenza a nuovi antibiotici come la daptomicina ed il linezolid è stata descritta, complicando le opzioni terapeutiche per le infezioni causate da questi microrganismi.

Conclusioni: Le misure di controllo finalizzate a ridurre l’incidenza delle colonizzazioni ed infezioni in ambiente sanitario dovrebbero includere: lavaggio delle mani con antiseittico o con un agente antiseittico idroalcolico, screening di routine degli isolati clinici per la resistenza alla vancomicina, culture di sorveglianza, isolamento da contatto per i pazienti con VRE ed antimicrobial stewardship.

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Corresponding author: Prof. Giovanni Battista Orsi, Department of Public Health and Infectious Diseases, Sapienza University of Rome, P.le Aldo Moro 5, 00185 Roma, Italy e-mail giovanni.orsi@uniroma1.it