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INFECTIOUS DISEASE

Glycopeptide resistant enterococci: What's the problem?

G. Birgand*

Infection control unit, University hospital, Lille, France

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A B S T R A C T

Enterococci are cocci gram-positive bacteria belonging to the bowel flora. Since the end of the 80s, glycopeptide resistant enterococci (GRE) have emerged in healthcare facilities. It has become a major public health issue in several countries. In USA, the rate of GRE was in 2003 about 30% of Enterococci isolated in intensive care units. In UK, 910 GRE bacteraemia has been reported by hospitals during 2007 with a majority of *Enterococcus faecium* owning the *vanA* phenotype. The emergence of the resistance to glycopeptides has increased difficulties in treating infected patients. Collectively, the potential transfer of the resistance gene to others pathogens like meticillin resistant *Staphylococcus aureus* is feared. The application of infection control guidelines and an appropriate use of antimicrobial agents could allow avoiding infections. This article had the aim to give an overview on problems associated to the spread of GRE and to provide some recommendation about the management of infected or colonized patients.

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1. Introduction

Enterococci belong to the resident flora of the gastrointestinal tract of humans. Under normal circumstances they are harmless commensals, and are even believed to have positive effects on a number of gastrointestinal and systemic conditions.[1] Enterococci are relatively poor pathogens, usually causing colonisation rather than infection. However, when the commensal relationship with the host is disrupted, Enterococci can cause invasive diseases.[2] Though not as virulent as other Gram-positive organisms, Enterococci can cause a variety of clinical syndromes in compromised patients including cholangitis, endocarditis, bacteraemia, meningitides, wound and urinary tract infections and are associated with peritonitis and intra-abdominal abcesses. The vast majority of clinical Enterococcal infections in humans are caused by *Enterococcus faecalis* in around 80% of clinical isolates and *Enterococcus faecium* in most of the remainder.[3] Enterococci are an increasingly common cause of Hospital Acquired Infections. In the USA, three to four nosocomial bloodstream infections per 10,000 hospital discharges are caused by enterococci, and contribute to patient mortality as well as additional hospital stay.[4]

The last few decades have seen the increasing emergence of resistant "superbugs" like glycopeptide resistant enterococci (GRE). This article is intended to give an overview on the consequences of the emergence and spread of GRE in healthcare facilities.

2. Emergence of multidrug resistant Enterococci

The emergence of antibiotics resistant organisms is a major public health issue and is the subject of international discussions. In the spread of new resistances in the community, as in healthcare facilities, it is important to take in to account the progressive decrease in the development of new antimicrobial agents.

In the USA, the first resistance to antibiotics acquired by Enterococci appeared during 70s with the emergence of *E. faecium* resistant to amoxicillin. Resistance to aminoglycosides then followed during the 80s. Consequently, glycopeptides have taken an increasingly large place in the arsenal of antimicrobials particularly for the treatment of infections due to meticillin resistant *Staphylococcus aureus* (MRSA). MRSA represents about one third of all *S. aureus* stains and this high rate leads to the use of glycopeptides.[5] The subsequent effect of this use is the emergence of resistant organisms to glycopeptides and resistance to vancomycin (the last active agent for multidrug resistant *E. faecium*) was first detected in Enterococci during mid 80s. Those emerging resistances have drawn attention to the potential difficulties in treating Enterococci infections now and in the future. While a major issue, GRE are not a high profile cause of invasive infection and certainly do not "enjoy" the same clinical, journalistic and hence political interest as MRSA and *Clostridium difficile*.

Of several resistance profiles, the *vanA* gene is the most frequent phenotype. It gives Enterococci a very high resistance level to both

* CHRU de Lille, Service de gestion des risques infectieux et des vigilances, Hôpital Calmette, Pavillon Christiaens, 59037 Lille, France.
E-mail address: birgand_gabriel@yahoo.fr

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vancomycin and teicoplanin. This gene is situated on a transposon and therefore it is highly transferable to others pathogens. The transmission of this glycopeptides resistance to other bacteria like *S. aureus*, which is pathogenic and widespread, is quite rightly, feared. In this way resistance developing in a relatively innocuous organism can result in a change in resistance profile of more virulent organisms. Vancomycin resistant *S. aureus* (VRSA) strains have already been described in USA.[6] In the United Kingdom, the high level of MRSA carriage increases the opportunity for resistance transfer and there is a high risk that VRSA emerging will emerge in Healthcare facilities. The spread of multiresistant strain of *S. aureus* would be a huge issue in the management of hospital acquired infections. These arguments demonstrate the potential importance of the emergence of GRE in healthcare units.

3. Epidemiology

The first strain of *E. faecium* with high resistance level to the glycopeptides, vancomycin and teicoplanin, was described in 1987.[7] The evidence is incomplete but, it is generally thought that the use of avoparcine as a food supplement in animal husbandry is associated with emergence of GRE in animal faeces. Then, those strains enter the food chain and can colonize humans.[8] The further administration of glycopeptides to patients after admission to hospital may then potentiate the subsequent emergence and spread of GRE. This may be compounded by cross-transmission between hospitalized-patients.[9] The emergence of Enterococci with acquired glycopeptide resistance is mainly the result of the appearance and spread of the resistant gene in an environment with high antibiotics usage such as acute care units.

The risk factors for GRE colonisation or infection commonly described are exposure to antibiotics, hematologic malignances, renal failure, transplant, prolonged hospital stay, exposure to intensive care unit.[10] The main site of colonisation is the large bowel. Ways of transmission between patients and healthcare workers are probably via hands, fomites or environmental contamination.

Since their first identification in USA in 1989–1990, GRE have become endemic in this country and, on the base of all data in 1998–2003, they were ranked third of the multidrug resistant bacteria in intensive care units.[11] In ITU, the rate of GRE among enterococci isolated has increased from 1% in 1989 to 28% in 2003. This increase probably reflects a convergence of risk factors including severe illness and antimicrobial therapy. The emergence of GRE during the mid 80s coincided with an increase in use of glycopeptides for MRSA, coagulase negative staphylococci and *C. difficile* diarrhoea.[12] Among antibiotics implicated in GRE colonisation or infection, cephalosporins, vancomycin and fluoroquinolones are the most cited antimicrobials.[13]

Data from the European antimicrobial resistance surveillance system show a rate of *E. faecium* isolated from GRE bacteraemia higher than 20% in several countries (Ireland, Portugal, Greece, United Kingdom…) and less than 1% in others countries like the Scandinavians countries. An increase of the resistance is also being seen in some countries such as Germany, Ireland, Israel, and Slovenia.

In the UK, GRE were first detected in 1986 and reporting of clinically-significant GRE bacteraemia has been mandatory for NHS acute Trusts in England since September 2003. Between October 2006 and September 2007, 910 GRE bacteraemia cases were reported by English hospitals. Among the acute National Health Service (NHS) Trusts that reported data, 24 (14%) reported >10 cases, 94 (55%) reported 1–10 cases, and 53 (31%) had no cases. The majority of Trusts reporting >10 cases were acute teaching Trusts. The proportion of Enterococcal bacteraemia attributable to GRE for the UK as a whole in 2007 were 8.5-12.5% for all Enterococci, 20 - 25% for *E. faecium* and 1.6–2.5% for *E. faecalis*. The majority of GRE in the UK are *E. faecium*, and that the bulk of GRE have the *VanA* phenotype, with non-susceptibility to both vancomycin and teicoplanin.[14] GRE bacteraemia isolates were most likely to be from patients who had been in hospital for more than 48 h, and were associated with haematology/oncology patients. Inter-centre variation of GRE prevalence was also highlighted, with 54.1% of vancomycin non-susceptible isolates coming from just six out of all 29 centres participating in the study.[15]

4. Treatment

Two essential rules have to be known:

- Carriage of GRE doesn't need to be treated.
- Decontamination doesn't need to be performed for colonized patients.

4.1. Patients infected with glycopeptide resistant enterococci

Enterococci are poorly pathogenic and far more frequently cause colonisation than infections. A clinical assessment of patient is needed to distinguish when antimicrobial therapy or others interventions become necessary.

GRE infections may be associated with urinary or intravenous catheters, correct management for which, often entails their removal. Source control may be essential and wounds may need debridement and abscesses may need drainage whenever possible. For gastrointestinal tract pathology and hence polymicrobial bacteraemia, antimicrobial therapy need to be directed against the other bacteria.

It is highly advised to reduce the use of glycopeptides and to limit prescriptions of third generation cephalosporins (particularly the ceftriaxone). When a patient is infected or colonized by GRE, a screening for MRSA with a nasal swab is recommended. When the patient is colonized with MRSA, decontamination with mupirocin in nasal during 5 days and a shampoo with chlorexidine are also recommended.

When antimicrobial treatment of GRE is considered necessary, a drug should be selected as determined by the susceptibility testing of the organism involved. The majority of *E. faecalis*, including glycopeptide resistant strains, still remains sensitive to ampicillin otherwise the main treatment of documented GRE infections is Linezolid, Zyvox® in monotherapy (by mouth 600 mg every 12 hours usually for 10-14 days max. duration of treatment 28 days or by intravenous infusion over 30–120 min, 600 mg every 12 h) except for endocarditis. When Linezolid can't be used, the Tigecyclin, Tygacil® (intravenous infusion for adults over 18 years initially 100 mg, then 50 mg every 12 h for 5–14 days) could be a solution. Quinupristine/dalfopristine (Synercid®) is a streptogramin with a bactericidal activity against GRE. However, Synercid® is an intravenous medication requiring slow infusion within a large volume of fluid and this administration method is a major inconvenient in it use (Adult over 18 years, by intravenous into central vein, 7.5 mg/kg every 8 hours and duration of treatment depends on site of infection). The Daptomycine (Cubicin®) is bactericidal and could be used against GRE but possess poor activity against *E. faecalis*. Some cases of GRE bacteraemia have been treated successfully with Daptomycin (4 mg/kg in 0.9% sodium chloride over a 30-minute period once every 24 h for 7–14 days).

4.2. Antimicrobial agents development

Some antibiotics are in the clinical efficacy trial phase. Oritavancin, a glycopeptide active on GRE, is in the late phases of clinical trials.

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Dalbavancin is a lipoglycopeptide with better MIC ranges than vancomycin for susceptible strains and have the convenient to be administered once a week. However, this agent has generally a suboptimal activity against *vanA* phenotypes. The Telavancin, ramoplanin is more bactericidal than vancomycin. In vitro, Telavancin has displayed activity against Enterococcus species but with a relatively high MIC_{90} against GRE compared to results obtained against sensitive strains. Finally, Avilamycin and evernimicin (Ziracine®) are others drugs active against GRE and which could be used in the future for infections due to multiresistant gram-positive cocci.

4.3. Patients colonized with glycopeptides resistant enterococci

Faecal carriage of GRE can persist for month or years and GRE carriers are often recurrently admitted patients. They are potential sources of cross-transmission. A number of attempts have been made to clear stool carriage of GRE but none of those can totally decolonize patients.

5. Infection control

For the many reasons described previously, the control of emergence and spread of GRE is essential. Effective hand hygiene is still the most important measure to prevent the spread of antimicrobial-resistant organisms. Hands should be systematically decontaminated between each patient contact including after removal of gloves whether or not the patient is known to be colonized with GRE.[16] Ideally, patient with GRE should be isolated in single rooms or, if it is not possible cohorted in bays in open ward. The risk of transmission is increased by presence of diarrhoea or incontinence. Those patients must be isolated to prevent the spread of GRE to others and to reduce the environmental contamination.[17] When a patient is transferred to another ward or another hospital, the clinician team or the infection control team should inform the receiving clinician and infection control staff of the patient's GRE carriage status. Finally, a review of the antimicrobial usage and policies in addition to audits are known to be efficient in the control of GRE colonisation or infection outbreaks.

6. Essential messages to keep in mind about GRE

- There is a risk of the spread of glycopeptide resistance from GRE to MRSA strains.
- A patient known as infected or colonized by GRE need to be considered as such even if samples remain negatives.
- Third generation cephalosporins are totally inactive against Enterococci and can select GRE.
- Infection with Enterococci sensitive to amoxicillin need to be treated with it.
- Inappropriate glycopeptides use (wrong indications, long treatments, low doses…) select GRE. Infection with meticillin sensitive *S. aureus*, should be treated with flucloxacillin (penicillin M).
- Keep antibiotic treatments only for documented infections and when other actions don't work. Usual treatment is the Linezolid (Zyvox®) or Tigecyclin (Tigacyl®) when the Linezolid can't be used.
- All antibiotic treatment needs to be revaluated after 48–72 h and 7–10 days of treatment are usually enough (except endocarditis and bone infections).

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