WORKING PARTY REPORT

Guidelines for the control of glycopeptide-resistant enterococci in hospitals


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KEYWORDS
Glycopeptide-resistant enterococci; GRE; Hospital infection; Infection control; Guidelines

Summary  The increase since the mid 1980s in glycopeptide resistant enterococci (GRE) raised concerns about the limited options for antimicrobial therapy, the implications for ever-increasing numbers of immunocompromised hospitalised patients, and fuelled fears, now realised, for the transfer of glycopeptide resistance to more pathogenic bacteria, such as Staphylococcus aureus. These issues underlined the need for guidelines for the emergence and control of GRE in the hospital setting. This Hospital Infection Society (HIS) and Infection Control Nurses Association (ICNA) working party report reviews the literature relating to GRE prevention and control. It provides guidance on microbiological investigation, treatment and management, including antimicrobial prescribing and infection control measures. Evidence identified to support recommendations has been categorized. A risk assessment approach is recommended and areas for research and development identified.

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Introduction

In 1995, the Hospital Infection Control Practises Advisory Committee (HICPAC) in the USA published recommendations for preventing the spread of vancomycin resistance in enterococci. These recommendations included the control of vancomycin usage, detection of glycopeptide-resistant enterococci (GRE) in patient populations and rectal surveillance culture to detect patients colonized with GRE, followed by contact isolation with gowns and gloves. Shortly after publication of the HICPAC recommendations, a GRE Working Party was convened by the Hospital Infection Society (HIS). However, this GRE Working Party was unable to make any recommendations because of the paucity of experience and published evidence outside the USA.

These guidelines were developed by a joint working party of the HIS and Infection Control Nurses Association (ICNA) (a list of those involved appears at the end of this report) that met between 1999 and 2001. To inform the work of the group, an ICNA member (PH) telephoned 30 UK infection control nurses in 1998 to ascertain their approach to GRE control. Only seven had a written GRE control policy and approaches were based on pragmatism, practicalities, experience and cost-effectiveness without review of available evidence.

There has been much debate about the evidence categorizations used in systematic reviews. We have used a system devised by others in the UK to grade the evidence underpinning guideline recommendations. This has been used in the infection control guidelines developed by the Thames Valley University.†

- Category 1: generally consistent findings in a range of evidence derived from well-designed experimental studies.
- Category 2: evidence based on a single acceptable study, or a weak or inconsistent finding in several acceptable studies.
- Category 3: limited scientific evidence that does not meet all the criteria of ‘acceptable studies’, or an absence of directly applicable studies of good quality. This includes published or unpublished expert opinion.

This is an evolving area and we note that another UK working party has used another categorization scheme for their published guidelines.

In reviewing the published literature to underpin the proposed statements, Medline and EMBASE databases were used. The following key words were used in searches: Enterococcus, Enterococcus faecalis, Enterococcus faecium, vancomycin resistant enterococci, glycopeptide resistant enterococci, VRE, GRE, vancomycin resistance, glycopeptide resistance, outbreak, vanA, vanB, vanC, vanD, vanE, disinfectants, antibiotics, antimicrobials, screening, isolation, typing, genotype, genotyping, phenotype, phenotyping, AFLP, PFGE, PCR, MLST and microchips. Different members of the Working Party led for different sections of the report. Abstracts were read and papers were further examined if they described GRE outbreaks in hospitals and relevant aspects of the guidelines were mentioned, e.g. media, isolation, screening and typing. We used a similar approach as that used in the Health Technology Assessment (HTA) methicillin-resistant Staphylococcus aureus (MRSA) systematic review regarding the assessment of the scientific rigour of papers, although we were not funded to apply this as we would have liked (two members reading every paper and a third settling disputes). Instead, repeated controlled draft documents were sent to all members via E-mail and expert consensus was established. The literature searches were updated in response to specific queries from our parent bodies in 2003-2004.

Initial drafts of the various parts of the document were repeatedly circulated within the group and consensus guideline statements were agreed. For comment, the draft document was then lodged on the HIS website in November 2001 and sent to the councils of the parent bodies, all employees of the Public Health Laboratory Service with access to E-mail, and all members of the European Society of Clinical Microbiology Study Group on Nosocomial Infection and the HARMONY infection control group (http://www.harmony-microbe.net/microtyping.htm). The guidelines are intended for adult patients in the acute setting. It was thus also sent to relevant professional societies such as those representing renal, haematology and intensive care unit (ICU) practitioners. We requested submission of any additional references confirming or refuting statements, or unpublished data felt to contribute significant evidence to inform these guidelines.

The proposed guidelines were well received. We were asked to provide more definitive guidance on how to define a GRE-associated outbreak and to be more prescriptive about outbreak interventions. However, the Working Group was of the opinion that the risk assessment approach advocated was all that could be recommended until there was
more definitive evidence. This approach received further support at a workshop discussion held at the International HIS Conference in October 2002 in Edinburgh.

In 2003, we responded to proposals from the councils of the ICNA and HIS to use the AGREE criteria on the Scottish Intercollegiate Guidelines Network (SIGN) website (www.sign.ac.uk). On this site, it is pointed out that appraisers should 'bear in mind that it is unlikely that any guidelines will meet all of the criteria in full: the AGREE criteria represent something of an ideal methodology, which SIGN and other guideline developers are striving to meet. However, by using this guide, we hope that those appraising SIGN guidelines against the AGREE criteria will find it easier to access the information required to make a fair and valid assessment'.

In the process of finalising this document, several areas for research and development were identified and have been included. We were not funded to perform a systematic review with epidemiological and economic modelling as in the HTA MRSA systematic review.8 This latter group produced recommendations for outbreak reports and intervention studies (Appendix 5 of Ref. [8]). The GRE Working Party Chairman (BC), also a member of the MRSA systematic review group, realized that most of the papers reviewed would not satisfy these recommendations. Since the first draft of this report, an important systematic review has been published on the effects of antibiotics on the epidemiology of GRE9 and also mentioned many of the confounding factors outlined in the MRSA review.8

The MRSA review group8 was also critical of the ways in which the economic aspects of studies had been addressed. The Working Party would envisage that our recommendations are considered further by our parent bodies, the Department of Health and various research councils. Amongst these considerations should be the applicability of the findings and methodologies of the MRSA systematic review8 to a similar review of GRE prevention and control measures. We envisage that these guidelines will need to be revised in 2006.

Background

Enterococci colonize the bowels of most normal people in concentrations of up to 10^7 colony-forming units/g of stool.10,11 Although there are 21 recognized species of enterococci,12 E. faecalis predominates as a human commensal and accounts for about 90% of clinical isolates. In recent years, E. faecium has been seen with increasing frequency, probably because of its greater antibiotic resistance.13,14 Other species of enterococci are isolated infrequently from humans. Most clinical isolates represent colonization rather than infection, which is typically endogenous. 13 Enterococci most commonly cause infections of the urinary tract, but also of the abdomen and pelvis where they may be found mixed with other bowel flora.13,14 They are relatively poor pathogens but may cause invasive disease in compromised patients, causing bacteremia (sometimes polymicrobial), wound infection, cholangitis, endocarditis and meningitis.13,14

Enterococci are now the third most common cause of hospital-acquired infection (HAI), being responsible for 10-12% of all HAIs, 10-20% of hospital-acquired urinary tract infections and 5-10% of hospital-acquired bacteraemias.15,16 In hospital infections, the reservoir of enterococci is usually the patient’s bowel. Nevertheless, cross-infection and clusters of infection occur and the emergence of resistant strains (glycopeptide resistant or high-level aminoglycoside resistant) have informed our understanding of the dynamics of their spread via staff hands and occasionally the environment.17–20 As with outbreaks of many other antimicrobial-resistant organisms, colonization is more frequent than true infection. The epidemiology is discussed below.

Summary

Enterococci are commensals of the human bowel.

E. faecalis is the predominant commensal species of humans and causes about 90% of infections; E. faecium is isolated with increasing frequency.

Enterococci are relatively poor pathogens, usually causing colonization rather than infection.

Most enterococcal infections are endogenous, but cross-infection between hospitalized patients does occur.

Enterococci are frequently isolated in mixed culture and their clinical significance is sometimes doubtful.

Enterococci are an increasingly common cause of HAI.

Glycopeptide resistance

Glycopeptide antibiotics inhibit synthesis of Gram-positive cell walls. By binding to the D-alanyl-D-alanine terminal sequences of the muramyl
The action of polymerases and peptidases involved in cell wall synthesis. As most clinically important Gram-positive bacteria are susceptible to glycopeptides, they have become agents of choice and the last resort for treating infections with multi-antibiotic-resistant organisms. Susceptible bacteria usually have vancomycin minimal inhibitory concentrations (MICs) in the range of 0.5-4.0 mg/L; teicoplanin MICs are similar or slightly lower. Acquired glycopeptide resistance can be divided into 'low level' (vancomycin MICs: 8-32 mg/L) and 'high level' (vancomycin MICs: ≥ 64 mg/L). However, there are several resistance phenotypes, the mechanisms and genetics of which have been reviewed by Woodford et al. and Leclerq and Courvalin. High-level, inducible, transferable resistance to both vancomycin and teicoplanin is now called VanA, and low-level inducible resistance to vancomycin alone is called VanB. VanA resistance is usually plasmid-borne but, encoded on a vanA transposon, may become incorporated into the chromosome. VanB resistance is usually chromosomal but, encoded on a vanB conjugative transposon, occasionally transfers to other strains of enterococci directly or by a plasmid. Both VanA and VanB resistance are most commonly seen in E. faecium and E. faecalis. Constitutive low-level vancomycin resistance, encoded by the vanC genes, is found in strains of Enterococcus gallinarum and related resistance genes have been reported in Enterococcus casseli- flavus and Enterococcus flavescens. There are many variants of these basic phenotypic patterns; most appear to result from the presence of altered bacterial ligases which replace D-alanyl-D-alanine terminal sequences with D-alanyl-D-lactate or D-alanyl-D-serine with reduced binding affinity for glycopeptides. The vanA or vanB resistance genes are very different in base composition and, thus far, their microbial origins are unknown. VanA resistance has been transferred in the laboratory and on animal skin to other Gram-positive bacteria, including S. aureus. This potential for gene transfer has now been realized with reports of the first clinical isolates of vancomycin-resistant S. aureus in 2002 and in 2004.

There are several resistance phenotypes. VanA, with high-level resistance to both vancomycin and teicoplanin, is the most important and is encoded on a transposon that is often located on a transferable plasmid. The recently reported transfer of VanA resistance to the more virulent pathogen S. aureus is an important reason for controlling the emergence and spread of GRE.

The epidemiology of glycopeptide-resistant enterococci

The emergence of enterococci with acquired glycopeptide resistance is mainly the result of the appearance and spread of transposons encoding vanA and vanB genes, usually within environments where there is heavy usage of antibiotics, for example in renal, haematology, oncology, transplant and intensive care units. The Centers for Disease Control and Prevention (CDC) noted that the percentage of GRE implicated in nosocomial infections in ICUs increased from 0.4% in 1989 to 7.2% in 1997. This increase probably reflects a convergence of risk factors including severe illness and antimicrobial therapy. The emergence of GRE in the mid 1980s coincided with an increase in the global usage of glycopeptides for the treatment of MRSA and coagulase-negative staphylococci and Clostridium difficile diarrhoea. It is likely that GRE selection and spread are facilitated by increasing glycopeptide usage, although other antimicrobials have also been implicated. Vancomycin has been cited as an antimicrobial risk factor for GRE colonization or infection. In a recent study of 50 US ICUs, there was a fall in the incidence of GRE in units that reduced vancomycin usage, compared with a rise in those that did not (mean decrease of 7.5% compared with mean increase of 5.7%, P < 0.001). However, a meta-analysis of multiple studies from the USA and a controlled observational study failed to confirm the independent effect of vancomycin therapy. Cephalosporins are the most cited antimicrobial risk factor for GRE colonization or infection. Fluoroquinolones have also been implicated, as has preceding therapy with agents active against anaerobes, especially in the context of C. difficile-associated diarrhoea. Tokars et al. showed for the first time a stepwise increase in GRE prevalence with increasing total antimicrobial-days per patient (up to 120 days in long-stay wards); a factor that may be as important as the risk associated with specific agents

Summary

Acquired glycopeptide resistance has emerged in enterococci, in particular E. faecalis and E. faecium.
themselves. Before this study, it was known that patients were more likely to acquire GRE if their length of hospital stay was prolonged. The effect of length of stay, antibiotic exposure, control groups and publication bias in studies of antimicrobial risk factors is an area of continuing debate, as it has also been for MRSA. GRE are encountered more frequently in teaching hospitals and in hospitals with a higher complement of beds; a 1993 survey conducted by the CDC showed a GRE prevalence of 3.6% of enterococci in hospitals with > 500 beds, 1.8% in hospitals with 200-500 beds, and 0% in hospitals with <200 beds. Presumably the higher occurrence of GRE in these hospitals is related to their more complex case-mix.

In Europe, GRE are found in the bowels of normal people in the community, in frozen meats and animal carcasses, and in the bowels of animals fed the glycopeptide avoparcin as a food supplement. Although there is considerable debate and the scientific evidence is incomplete, it is generally accepted that the use of avoparcin as an ergotropic agent in animal husbandry is associated with the emergence of GRE in animal faeces. At least some of these strains then enter the food chain and colonize humans. Administration of glycopeptides may result in the subsequent emergence of GRE following hospital admission. GRE may also spread by cross-infection between hospital patients and (presumably) within community cohorts. In addition, transposons encoding glycopeptide resistance probably transfer between commensal enterococci in animal and human gut. However, in the USA, avoparcin has not been used as an ergotrope, so GRE are not thought to have entered the food chain and colonized the general population. Nevertheless, nosocomial GRE colonization and infection appear to be much more frequent in the USA than in Europe.

Alert organism surveillance from routine clinical specimens is the usual method of GRE surveillance in the UK, although a variety of forms of GRE surveillance are undertaken at specific centres. A recent study of blood isolates in England and Wales has shown that vancomycin resistance in E. faecium increased from 6.3% in 1993 to 24% in 1998, whereas in E. faecalis it increased from ~3% in 1996 to 5% in 1998. In the USA and Canada, several workers have suggested that, as many of the antimicrobials that select for C. difficile also select for GRE, faecal specimens submitted for C. difficile toxin testing might also be examined for GRE. This approach is interesting although it is no substitute for screening of patients during outbreaks. In a recent study, 32% of stool specimens from hospitalized patients submitted to a diagnostic laboratory in the UK yielded GRE, with carriage increasing with age. The carriage rate in community specimens, made up of general practice patients and food handlers, was 2.3%.

The most common site of GRE colonization is the large bowel. Colonization can be prolonged, often for months and sometimes for years. It is possible that colonization may be persistent, even whilst non-enrichment screens for GRE are negative (See Screening for glycopeptide-resistant enterococci). GRE have been isolated from swabs of faeces, rectum, throat, vagina and skin. The main routes of transmission between patients and healthcare workers are probably via hands, fomites and/or environmental contamination. Enterococci may contaminate the environment around a patient and survive there for several days, and environmental contamination is increased when patients have diarrhoea. Surfaces or fomites (including medical instruments and equipment) that come into contact with staff hands may also become contaminated. These environmental sites are potentially secondary sources for cross-infection. However, several studies have failed to find epidemic strains of enterococci in the hospital environment and the recovery of environmental isolates is dependent on culture method. Environmental screens must therefore be interpreted with care.

Strains of GRE originating in the community are usually of multiple types, whereas hospital-associated outbreaks may result from either single or multiple strains. Elucidating the epidemiology will usually require molecular typing methods. Infection control measures will vary and reflect the epidemiology of the particular outbreak.

Further studies are needed on the incidence or prevalence of GRE in the community in the UK. Studies in Germany and Denmark indicate that the occurrence has decreased since the ban of avoparcin and other growth promoters. Hospitals with recurrent problems with GRE should consider implementing ongoing surveillance of GRE in stool specimens sent for culture. The cost-effectiveness of different surveillance strategies should be addressed, e.g. screening of those patients with previous hospital admissions, recent antibiotic administration or admissions to affected units, with suspected C. difficile diarrhoea or with known risk factors for GRE acquisition during outbreaks.

Summary

The emergence of GRE has occurred at a time of increasing glycopeptide usage.
The lower gastrointestinal tract is the most important reservoir. In Europe, animal strains of GRE may colonize the bowels of normal humans repeatedly via contaminated food. Risk factors for hospital infection with GRE include prior antibiotic therapy (especially with glycopeptides or cephalosporins), prolonged hospital stay, and admission to intensive care, renal, haematology or liver units. Transmission within hospitals is mainly on hands contaminated by contact with colonized or infected patients, contaminated surfaces, or fomites. Community strains are usually of multiple types; hospital outbreaks can involve single or multiple strains.

### Microbiological investigations

#### Screening for glycopeptide-resistant enterococci

Screening patients identifies colonization, elucidates the epidemiology and permits introduction of appropriate preventative measures, including isolation. The GRE Working Party suggests screening during suspected outbreaks (two new cases of GRE detected in clinical specimens related in time and place) and in response to important incidents (defined on the basis of risk assessment as outlined elsewhere in this report). It can be assumed that patients who are clinically infected with GRE are already colonized in the gastrointestinal tract.76 The screening specimen with the greatest yield is the stool.76 GRE may not be detected in rectal swabs from some patients, and Wade75 emphasized the importance of including all clinically relevant sites when screening patients for GRE carriage. Colonized sites other than faeces include the throat, skin, vagina, perineum, wounds, urine and vascular catheter sites.43,45,76

The laboratory culture method employed will affect the yield from screening specimens; the use of a selective medium is recommended.1,27 Media usually consist of a selective agent or agents, such as sodium azide, an antimicrobial (usually nalidixic acid, an aminoglycoside, a β-lactam agent, a polymyxin or a combination of these) or bile salts, and an indicator such as aesculin or a tetrazolium agent. A wide range of selective media has been investigated but there is no agreement on which is the best.87 Some incorporate high concentrations of vancomycin (20-64 mg/L), which will inhibit some strains with low-level resistance, and 6 mg/L probably offers the best compromise between sensitivity and specificity. The current National Committee for Clinical Laboratory Standards method88 for screening isolates of enterococci for glycopeptide susceptibility utilizes vancomycin at 6 mg/L. When screening for GRE, a dedicated indicator medium, such as Enterococcus sel agar with 6 mg/L vancomycin (or a medium with equivalent performance), is recommended. However, none of the media investigated are completely specific, and suspect colonies should be confirmed as GRE by identification and glycopeptide susceptibility testing by a recognized method.88,89 The use of enrichment broth increases GRE detection rates90,91 but the significance of this increase in sensitivity for outbreak management is unclear. The technical expertise, time and additional consumables needed to confirm the identification of isolates grown from selective media adds significantly to the expense.

There is a pressing need for improved media to reduce the burden on the laboratory for the detection and identification of GRE. Alternatively, molecular techniques, which might even be used at the bedside, may prove to be cost-effective, and a greater priority should be given to the development of such approaches.

**Summary**

Screening to identify colonized patients is recommended during outbreaks (Category 3). The most frequent site of colonization is the large bowel, and faeces is the most useful screening specimen. Additional colonized patients may be revealed by screening other sites, e.g. wound and vascular catheter sites (Category 1). A selective medium should be used for screening for GRE carriage (Category 1). A wide range of selective media has been investigated but there is no agreement on which is the best. Enrichment culture increases GRE detection rates (Category 1) but is not essential for the management of most outbreaks (Category 3).

**Typing**

Laboratories may recognize local outbreaks of GRE in the presence of characteristic or unusual biotypes or antibiograms. However, these markers are not discriminatory and, because of the
complex epidemiology, further typing is required. 

Many typing systems have been applied to enterococci. Classical phenotypic methods such as serotyping and phage typing were largely designed for *E. faecalis* and have been replaced by a wide variety of DNA-based methods applicable to all species of enterococci. More recent methods include amplified fragment length polymorphism (AFLP) and, for *E. faecium*, multi-locus sequence typing (MLST). These both need to be assessed more rigorously with GRE collections including those from outbreaks. In recent years, pulsed-field gel electrophoresis (PFGE) has become the method of choice for the epidemiological analysis of many types of nosocomial infection, including GRE. However, there are no universally agreed standard criteria for interpreting PFGE banding patterns and there are problems with inter- and intralaboratory reproducibility. Enterococci are a particular problem because single strains may show considerable genetic polymorphism both in the genome and the vanA composite transposon.

When local typing of GRE produces results that are difficult to interpret, isolates should be sent to reference laboratories with expertise in this area. Selection of isolates being sent to the reference laboratory is a matter for discussion between the referring laboratory and the reference laboratory. A genetic factor (*esp*) was described as being related to epidemicity of enterococci. However, there is some doubt regarding its sensitivity, and further work is needed to explore its applicability as a potential risk assessment indicator to inform outbreak control measures.

There is no ideal typing method for GRE, and newer approaches need to be assessed on collections of organisms designed to represent the common or important epidemiological problems encountered by infection control teams. If epidemic, virulence and typing markers could be identified and added to others that will identify GRE, this would add further to the cost-effectiveness of such methods in the clinical laboratory setting.

**Summary**

In order to elucidate the epidemiology of GRE, isolates from both infected and colonized patients should be typed (Category 3). No typing method is ideal for GRE, but PFGE is currently considered optimal (Category 1). Where there is no local facility for typing, it will be necessary to send isolates to a reference laboratory.

**Treatment and management**

**Patients infected with glycopeptide-resistant enterococci**

Enterococci are poorly pathogenic and frequently cause colonization rather than invasive infection. The healthcare team should assess each patient to distinguish between colonization and infection and then decide whether antimicrobial therapy and/or other interventions are necessary.

GRE infection of the blood or urinary tract may be associated with intravenous and urinary catheters, respectively, and correct management often entails removal of the catheter. Wounds may need debridement and abscesses may need drainage wherever possible. GRE are often associated with gastrointestinal tract pathology and hence polymicrobial bacteraemia, in which case the underlying condition must be addressed with antimicrobial therapy also directed against the other bacteria.

If after clinical assessment and primary management, antimicrobial treatment of GRE is considered necessary, a drug should be selected based upon susceptibility testing of the organism involved. Nearly all strains of *E. faecalis*, including glycopeptide-resistant strains, are susceptible to ampicillin. GRE often remain susceptible to tetracycline, chloramphenicol or rifampicin and there have been anecdotal reports of successful treatment with these agents.

In addition, a number of new agents with potential use for GRE infections are available, including the streptogramin combination, quinupristin/dalfopristin (which, however, is not active against *E. faecalis*), and the oxazolidinone, linezolid. However, resistance to the latter agent has already been described in some *E. faecium* isolates. The role of these and other agents in development awaits further assessment.

**Summary**

Colonization with GRE is much more frequent than infection and patients must be reviewed before commencing antimicrobial therapy (Category 1).
Management of GRE may include removal of catheters and drainage of abscesses (Category 3).
Glycopeptide resistance reduces the therapeutic options for enterococcal sepsis.
The choice of antimicrobial therapy should be guided by susceptibility testing.
Where GRE are part of polymicrobial bacteraemia, antimicrobial therapy should also be directed at the other pathogens.
New agents are available and are undergoing clinical evaluation. Resistance is already described and their use must be considered in this light.

Infection control measures

Principles of outbreak management

It is important to control the emergence and spread of GRE for the reasons stated previously: the limited therapeutic alternatives, the increasingly compromised inpatient population, and the potential for transfer of glycopeptide resistance to more pathogenic bacteria such as *S. aureus* (including MRSA). As already discussed, the epidemiology is complex; hospitals may be affected by sporadic cases of GRE, epidemics or endemic colonization and infection. Each of these situations will need to be managed in different ways, depending on the risk to the patients involved. Since enterococci are of low virulence and usually only cause serious infection in more compromised patients, the cost and risks of control procedures should be weighed against risks and benefits to the patient group concerned. One study has shown the cost of bacteraemia due to GRE to be $27 000 higher than that due to glycopeptide-sensitive enterococci.110

As with all other infection control interventions, the quality of clinical care must not suffer as a result of the precautions implemented. Due to the uncertainty surrounding the management of GRE, discussion between the infection control team and the clinical staff is essential. These issues are also discussed in relation to a recent outbreak in The Netherlands.111,112

A recent leader113 found that studies showing that the HICPAC recommendations were effective in controlling GRE far exceeded those where they failed. Effective control was reported in different clinical settings and where there were endemic problems. The HICPAC recommendations have been applied in the USA,113 the UK35 and South Africa.114 However, there may be an element of publication bias.

Control measures must be informed by a risk assessment. The Working Party thought that the risk assessment should include the extent of patient GRE colonization (including wounds, intravenous and urinary catheters), whether the patient is incontinent of faeces, whether the GRE are also resistant to other antimicrobials and which, the prevalence (and severity) of GRE colonization and infection, and the susceptibility to infection of patients on the affected wards. Risk assessment procedures have been considered by another UK working party. Their report entitled ‘Review of Hospital Isolation and Infection Control Related
Precautions’ is posted on the HIS website (http://www.his.org.uk/). A risk assessment tool [the Lewisham Isolation Priority System (LIPS)] is being assessed by several hospitals and is included in that report. We have illustrated the use of the LIPS for GRE in Table I.

The Working Party encourages infection control teams to publish their intervention strategies (e.g. improved antibiotic prescribing, hand hygiene, screening, surveillance, use of isolation strategies and designated staff) to prevent and control GRE outbreaks, including their risk assessment process. However, there are many biases and pitfalls in the design of infection control intervention studies that can cause problems in the interpretation of results. These have handicapped their potential to improve the evidence base needed to underpin prevention and control recommendations. These biases are described in detail in the HTA MRSA systematic review.

**Summary**

GRE colonization or infection may be sporadic, epidemic or endemic.

When cases of GRE are identified, the management strategy should be informed by a risk assessment that takes into account the background epidemiological pattern and the risk category of the patients involved (Category 3).

**Hand hygiene**

Effective hand hygiene is the most important measure to prevent and control the spread of antimicrobial-resistant organisms. Mathematical modelling has suggested that compliance with handwashing policies, significantly in excess of reported levels, or the cohorting of nursing staff is needed to prevent nosocomial transmission of GRE in endemic settings. Hands should be decontaminated between each patient contact, whether or not the patient is known to be colonized with GRE. The choice of handwashing materials is debated. In some studies, washing with soap and water, aqueous chlorhexidine or povidone iodine were unreliable for decontamination of GRE, but alcohol and alcoholic chlorhexidine were effective. Other studies have shown that handwashing with a chlorhexidine-based soap reduced the rate of nosocomial infections more effectively in an ICU than handwashing with sequential use of soap and alcohol, or with soap alone. However, Noskin et al. concluded that the duration of use of the soap was more important than the type of soap used. Current HICPAC guidelines recommend that healthcare workers should wash their hands with an antiseptic soap or use a waterless antiseptic agent when leaving the room of a patient with GRE. Alcohol-based solutions or gels are not cleansing agents and not recommended in the presence of ‘physical dirt’. Therefore, a waterless antiseptic agent may be appropriate during ward rounds or when additional hand hygiene is required. Many workers support the use of an alcoholic hand rub or gel because of its convenience and efficiency. Where patients are being nursed on an open ward, dispensers containing these materials should be readily available, some advocating them by every patient bedside and close contact area, an approach adopted by the recent pilot of the CleanYourHands campaign of the National Safety Agency (http://www.npsa.nhs.uk/cyh/campaign.jsp). Healthcare workers must use a technique which ensures that all parts of their hands are covered.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Reason in setting of GRE</th>
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<tbody>
<tr>
<td>ACDP category of containment level</td>
<td>5</td>
<td>Level two pathogen</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>5</td>
<td>Transmission by contact</td>
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<tr>
<td>Evidence for transmission</td>
<td>10</td>
<td>Published or strong evidence</td>
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<td>Significant antibiotic resistance</td>
<td>5</td>
<td>Glycopeptide resistance</td>
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<tr>
<td>Susceptibility of other patients</td>
<td>0 to 10</td>
<td>None (0) to susceptible with serious consequences (10)</td>
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<tr>
<td>Prevalence of infection in the hospital</td>
<td>−5 or 0</td>
<td>Endemic or epidemic (−5) to sporadic (0)</td>
</tr>
<tr>
<td>Dispersal characteristics</td>
<td>0, 5 or 10</td>
<td>Varies from low risk to high risk (e.g. faecal incontinence, droplet transmission)</td>
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<tr>
<td>Total for a patient with GRE</td>
<td>20 to 45&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> Advisory Committee on Dangerous Pathogens (1995) classification.

<sup>b</sup> The need for isolation is based on the final score, but can be set locally. University Hospital Lewisham use the following scores: 0–20, low priority for isolation; 25–35, medium priority; 40–50, high priority.
Summary

Hands should be decontaminated between each patient contact, including after removal of gloves (Category 3). Soap may not be as effective as disinfectant-containing preparations (Category 2). Alcoholic hand rubs or gels are more convenient than other hand disinfectants and can be used as the sole agents for hands provided that they are not visibly soiled (Category 1). Hand hygiene should be reinforced in the outbreak setting (Category 3).

Isolation of patients and environmental cleaning

The decision to isolate individual patients affected by GRE should be based on the clinical needs and risk assessment described above. Ideally, patients colonized or infected with GRE should be source isolated in single rooms. However, where there are larger patient numbers and insufficient isolation rooms, patients should be cohorted in bays on the open ward. Patients with GRE and diarrhoea or incontinence are at a higher risk of spreading GRE and must be given priority for single rooms.47

Even in the absence of known hospital infection, it should be hospital policy to clean the ward environment regularly to maintain proper standards of hospital hygiene.128 During GRE outbreaks, the ward environment may become heavily contaminated47,64,79 and will need further thorough cleaning following the discharge of the patients. There is no evidence that one cleaning regimen is better than another for eliminating GRE. The choice of cleaning regimen will depend on local policy (Category 3).

Transfer of patients with glycopeptide-resistant enterococci

When a patient with GRE is transferred to another hospital, the clinical team and/or infection control team responsible for the patient should inform the receiving clinical and infection control staff of the patient’s GRE carriage status. This allows the receiving institution to take necessary measures to protect vulnerable patients. In general, GRE neither present a risk to normal people in the community, nor to patients in residential or nursing homes who do not have catheters, wounds or other lesions.

Summary

If a patient with GRE is transferred to another healthcare institution, the receiving clinical and infection control staff should be informed (Category 3).

Control of antibiotic usage

The emergence and spread of GRE is encouraged by the use of certain antimicrobials. As discussed earlier, the use of the glycopeptide avoparcin in animal feed has been implicated in the emergence of GRE in animal stools, and the use of this agent in European farming was banned in April 1997. In hospital practice, the acquisition of GRE has been associated with antimicrobial administration, especially cephalosporins and glycopeptides.27 It is good clinical practice not to use any antimicrobial unnecessarily and clinical units should have appropriate policies for prudent antimicrobial use in...
Hospitals or units affected by GRE should review their antimicrobial usage and alter their policies, if necessary. On one haematology unit, the control of GRE was facilitated by the change from ceftazidime to piperacillin/tazobactam for the treatment of febrile neutropenic sepsis.\textsuperscript{38}

Although there is no experimental evidence to prove a causal relationship between glycopeptide usage and the emergence of glycopeptide resistance, many authorities recommend the control of glycopeptide use, and hence selection pressure, as an important element for the control of GRE.\textsuperscript{1} Hospitals should audit and review their policies, which should aim to avoid glycopeptide usage wherever possible. Appropriate glycopeptide usage includes prophylaxis or treatment of MRSA infections, treatment of serious infections in patients allergic to alternative antimicrobials, treatment of serious \textit{C. difficile} toxin positive diarrhoea unresponsive to metronidazole, and prophylaxis of endocarditis as recommended by the guidelines of the British Society of Antimicrobial Chemotherapy.\textsuperscript{133}

**Summary**

The emergence and spread of GRE appears to be encouraged by the use of antimicrobial agents, especially glycopeptides and cephalosporins (Category 1). All hospitals should have policies in place for prudent antimicrobial usage in all areas of clinical practice (Category 3).

**Acknowledgements**

The Hospital Infection Society and Infection Control Nurses Association GRE Working Party members were: Professor B.D. Cookson (Chairman; HIS: Medical and Reference Microbiology, Epidemiology and Infection Control); Dr M.B. Macrae (Secretary; HIS: Medical Microbiology and Infection Control); Dr S.P. Barrett (HIS: Medical Microbiology and Infection Control); Dr D.F.J. Brown (HIS: Clinical Microbiology Scientist); Ms C. Chadwick (ICNA: Infection Control); Professor G.L. French (HIS: Medical Microbiology and Infection Control); Mr P. Hateley (ICNA: Infection Control); Dr I.K. Hosein (HIS: Medical Microbiology and Infection Control) and Dr J.J. Wade (HIS: Medical Microbiology and Infection Control).

**Summary statements**

Where statements are guideline recommendations, they were categorized as follows:

- **Category 1**: generally consistent findings in a range of evidence derived from well-designed experimental studies.
- **Category 2**: evidence based on a single acceptable study, or a weak or inconsistent finding in several acceptable studies.
- **Category 3**: limited scientific evidence that does not meet all the criteria of ‘acceptable studies’, or an absence of directly applicable studies of good quality. This includes published or unpublished expert opinion.

**Background**

**Enterococci**

Enterococci are commensals of the human bowel. \textit{E. faecalis} is the predominant commensal species of humans and causes about 90% of infections; \textit{E. faecium} is isolated with increasing frequency. Enterococci are relatively poor pathogens, usually causing colonization rather than infection. Most enterococcal infections are endogenous, but cross-infection between hospitalized patients does occur. Enterococci are frequently isolated in mixed culture and their clinical significance is sometimes doubtful. Enterococci are an increasingly common cause of HAI.

**Glycopeptide resistance**

Acquired glycopeptide resistance has emerged in enterococci, in particular \textit{E. faecalis} and \textit{E. faecium}. There are several resistance phenotypes. VanA, with high-level resistance to both vancomycin and teicoplanin, is the most important and is encoded on a transposon that is often located on a transferable plasmid. The recently reported transfer of VanA resistance to the more virulent pathogen \textit{S. aureus} is an important reason for controlling the emergence and spread of GRE.
The epidemiology of glycopeptide-resistant enterococci

The emergence of GRE has occurred at a time of increasing glycopeptide usage. The lower gastrointestinal tract is the most important reservoir. In Europe, animal strains of GRE may colonize the bowels of normal humans repeatedly via contaminated food. Risk factors for hospital infection with GRE include prior antibiotic therapy (especially with glycopeptides or cephalosporins), prolonged hospital stay, and admission to intensive care, renal, haematology or liver units. Transmission within hospitals is mainly on hands contaminated by contact with colonized or infected patients, contaminated surfaces, or fomites. Community strains are usually of multiple types; hospital outbreaks can involve single or multiple strains.

Microbiological investigations

Screening for glycopeptide-resistant enterococci

Screening to identify colonized patients is recommended during outbreaks (Category 3). The most frequent site of colonization is the large bowel, and faeces is the most useful screening specimen. Additional colonized patients may be revealed by screening other sites, e.g. wound and vascular catheter sites (Category 1). A selective medium should be used for screening for GRE carriage (Category 1). A wide range of selective media has been investigated but there is no agreement on which is the best. Enrichment culture increases GRE detection rates (Category 1) but is not essential for the management of most outbreaks (Category 3).

Typing

In order to elucidate the epidemiology of GRE, isolates from both infected and colonized patients should be typed (Category 3). No typing method is ideal for GRE, but PFGE is currently considered optimal (Category 1). Where there is no local facility for typing, it will be necessary to send isolates to a reference laboratory.

Treatment and management

Patients infected with glycopeptide-resistant enterococci

Colonization with GRE is much more frequent than infection and patients must be reviewed before commencing antimicrobial therapy (Category 1). Management of GRE may include removal of catheters and drainage of abscesses (Category 3). Glycopeptide resistance reduces the therapeutic options for enterococcal sepsis. The choice of antimicrobial therapy should be guided by susceptibility testing. Where GRE are part of polymicrobial bacteraemia, antimicrobial therapy should also be directed at the other pathogens. New agents are available and are undergoing clinical evaluation. Resistance is already described and their use must be considered in this light.

Patients and staff colonized with glycopeptide-resistant enterococci

Stool carriage may persist for months or years. Attempts at clearance by oral therapy are usually unsuccessful and are not recommended (Category 1). Screening staff for stool carriage is of no value (Category 3).

Infection control measures

Principles of outbreak management

GRE colonization or infection may be sporadic, epidemic or endemic. When cases of GRE are identified, the management strategy should be informed by a risk assessment that takes into account the background epidemiological pattern and the risk category of the patients involved (Category 3).

Hand hygiene

Hands should be decontaminated between each patient contact, including after removal of gloves (Category 3). Soap may not be as effective as disinfectant-containing preparations (Category 2). Alcoholic hand rubs or gels are more convenient than other hand disinfectants and can be used as the sole agents for hands provided that they are not visibly soiled (Category 1).
Hand hygiene should be reinforced in the outbreak setting (Category 3).

Isolation of patients and environmental cleaning

The decision to isolate a patient should be based on the clinical risk assessment (Category 3). Ideally, patients with GRE should be isolated in single rooms or, if this is not possible, cohorted in bays on the open ward (Category 3). Patients with GRE and diarrhea or incontinence pose a high risk of GRE transmission to others and must be isolated (Category 2). Hospital wards should be cleaned regularly as part of a general programme of hospital hygiene (Category 3). After an outbreak or incident of GRE colonization or infection, isolation rooms (or the whole of a ward after more extensive outbreaks) must be cleaned thoroughly to reduce environmental contamination (Category 3). There is no evidence that one cleaning regimen is better than another for eliminating GRE. The choice of cleaning regimen will depend on local policy (Category 3).

Transfer of patients with glycopeptide-resistant enterococci

If a patient with GRE is transferred to another healthcare institution, the receiving clinical and infection control staff should be informed (Category 3).

Control of antibiotic usage

The emergence and spread of GRE appears to be encouraged by the use of antimicrobial agents, especially glycopeptides and cephalosporins (Category 1). All hospitals should have policies in place for prudent antibiotic usage in all areas of clinical practice (Category 3).

References


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