REVIEW

Controlling glycopeptide-resistant enterococci

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INTRODUCTION

Nearly 10 years have passed since the recognition of glycopeptide-resistant enterococci (GRE) as a clinical problem [1], and our knowledge of the epidemiology of these organisms has greatly increased. Despite this, there is comparatively little information available to guide our efforts in controlling GRE. Once GRE become established in a clinical area, they may cause a range of infections, associated with a high mortality, for which therapeutic options are limited. Moreover, there is potential for glycopeptide resistance genes to spread to other, more virulent organisms: gene transfer has already been achieved in vitro to produce a phenotypically vancomycin-resistant strain of *Staphylococcus aureus* [2]. For these reasons, strenuous efforts are warranted to minimize the spread of GRE. Until recently, the source of GRE (other than colonized patients in hospitals) was unclear. In 1994, Bates and colleagues isolated glycopeptide-resistant *Enterococcus faecium* from farm animals (including pigs and chickens), raw sewage and raw chicken [3]. From this and other reports it is now clear that GRE of the *vanA* genotype are present in animals and meat products in Europe, and that *vanA* resistance genes may be introduced into the community via the food chain. GRE may be entering the hospital environment via colonized individuals admitted from the community [4].

In North America, recommendations for the prevention of spread of glycopeptide resistance have been published by the Hospital Infection Control Practices Advisory Committee (HICPAC), in collaboration with the Centers for Disease Control and Prevention (CDC) [5]. These recommendations are based on four key elements: prudent vancomycin use; education of hospital staff; early detection and prompt reporting; and immediate implementation of infection control measures. The HICPAC recommendations may not be entirely applicable to practice outside the USA, due to differences in medical management and facilities, but they provide a useful basis for discussion of appropriate control measures from the perspective of UK practice.

ANTIBIOTIC POLICIES

Patients who are exposed to prolonged or multiple antimicrobial therapy are at risk of becoming colonized by GRE [6,7]. Moreover, certain antibiotics, particularly vancomycin [6,8,9] and cephalosporins [10], have been implicated in selecting for GRE. Although high levels of vancomycin may be achieved in the gut during oral vancomycin therapy [11–13], probably above those needed to kill GRE, levels will nevertheless tail off after treatment, potentially selecting for resistant strains both in patients and in the environment. The HICPAC guidelines advocate prudent use of vancomycin as a central measure in preventing the spread of vancomycin resistance, suggesting specific situations in which its use should be discouraged [5]. In Europe, where the glycopeptide drug teicoplanin is widely used, any proposed restrictions on the clinical use of vancomycin should also apply to teicoplanin. For this reason we favor the term 'glycopeptide-resistant enterococci' to the widely used 'vancomycin-resistant enterococci—VRE'. Situations in which we consider that glycopeptide drugs are not normally indicated are shown in Table 1.

Modifying the use of antibiotics other than glycopeptides has also been tried. For example, in a London outbreak [1] a switch from vancomycin and

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Table 1 Situations in which glycopeptide drugs are not normally indicated

First-line therapy for neutropenic sepsis
Continued empirical use when cultures are negative
First-line treatment of *Clostridium difficile* infection
Routine prophylaxis for surgery, neonates, dialysis, intravenous catheters
Convenience treatment of methicillin-sensitive organisms in renal failure
Single blood culture positive for coagulase-negative staphylococci
Eradication of methicillin-resistant *S. aureus* colonization
Selective decontamination of the gut
Topical application or irrigation

cephalosporins to flucloxacillin and aztreonam was thought to be helpful in controlling the outbreak, in combination with other measures (A. Uttley, personal communication).

EDUCATING HEALTHCARE WORKERS

Medical and nursing staff should be notified of the appearance of GRE at an early stage. This will enable an explanation of the problem to be given and should encourage cooperation in the subsequent efforts to control the organisms. In our experience, seminars held for healthcare workers on affected wards, reinforced by regular visits from the infection control team, have been useful in heightening awareness of infection control issues. Teaching should include: sources and modes of spread of GRE; handwashing technique; disposal of linen; assessment of patients for potential risk factors for cross-infection, such as diarrhea [14,15] and poor personal hygiene; and the importance of a clean environment [16]. Difficulties may be encountered in achieving and maintaining good practice in clinical areas, particularly in environmental cleaning (due to nursing and domestic shortages), and isolation of carriers and handwashing (due to lack of facilities) [17].

SCREENING FOR GRE

In studying the epidemiology of GRE, it is important to assess human carriage rates in different populations and to search for the organisms in the environment. Carriage rates have varied from relatively low levels up to 75% [18]. This variation is likely to reflect the type of patient and medical setting studied and will be a product of the recognized risk factors, such as antibiotic exposure, immunosuppression and intensive nursing. It is probable that apparent variations in carriage rate will also have arisen from differences in methodology, including protocols for screening (which sites, how often) and laboratory procedures, such as choice of media.

Screening patients

To date, few published studies have compared the recovery from different body sites when screening for carriage. Yamaguchi et al. studied 20 patients in a teaching hospital who were known to be colonized by glycopeptide-resistant *E. faecium* [19]. Swabs were obtained from nose, mouth, behind the ears, axillae, popliteal fossae and groins and plated directly onto Campylobacter agar. GRE were most frequently isolated from stools (95%); recovery from other sites was poor (25%). In a study of 46 patients on a liver unit, who were all known carriers of glycopeptide-resistant *E. faecium*, carriage was evaluated by screening mouth, nose, throat, rectum and perineum [20]. Swabs were plated both directly and after broth enrichment onto MacConkey agar. The 'full set' of screening swabs would have detected 80% carriers, rectal plus perineal swabs would have detected 69% and a rectal or perineal swab alone would have detected 61–63%. In a third teaching hospital, patients were screened prospectively for carriage during an outbreak of glycopeptide-resistant *E. faecium* colonization on a renal/hematology ward [21]. Specimens from nose, throat, axilla, perineum, hands and feces/rectum were cultured, with and without broth enrichment, on MacConkey agar and neomycin blood agar. Of the colonized patients, 26/29 (90%) would have been detected by culture of a perineal swab and feces/rectal swab. Further work is needed to evaluate optimum screening protocols for defined patient groups, but culture of feces/rectal swab and perineal swab (plus relevant clinical specimens) should provide a satisfactory, affordable screen. Infection control teams should formulate policies on which patients to screen for these organisms, at which sites and how often.

Choice of medium for screening

Various agar media containing vancomycin have been used to screen clinical specimens for GRE. Examples are colistin nalidixic acid agar [8], *Campylobacter* agar with clindamycin [22], kanamycin aesculin azide agar [4], neomycin agar [14] and MacConkey agar [20]. Insufficient comparative information is available at present to make a clear recommendation about which solid media perform best, for screening either patients or the environment. We have found neomycin blood agar to be unsatisfactory for screening fecal specimens [23], while aztreonam–amphotericin blood agar [24]

and bile-aesculin–Polymixin B agars, both containing vancomycin, have performed well (unpublished data). Finally, the use of broth-based media needs consideration; Landman and colleagues compared five different procedures for recovering GRE from perianal swabs and found Enterococcosel broth (containing bile–aesculin and sodium azide), supplemented with aztreonam and vancomycin, to be more sensitive than three agar media [25]. In a comparison of cephalexin–aztreonam–arabinose agar [26] and cephalexin–aztreonam broth, broth enrichment was found to more than double the yield from a mixture of patient and environmental specimens [27]. Further comparative studies of solid and broth-based media are urgently needed.

Screening healthcare workers

There is little evidence to implicate staff in transmission of GRE. In one report a nurse had to be removed from duty before an outbreak due to a multiply-resistant (but vancomycin-sensitive) *Enterococcus faecalis* could be terminated [28]. In a second report, exposure of patients to a nurse who looked after a known GRE-colonized patient on the same shift was associated with acquiring an outbreak strain [14]. Screening of healthcare workers has only been recommended if a clear epidemiologic link with transmission can be shown [5].

Eradication of asymptomatic carriage

The observation that large numbers of individuals can be colonized by GRE for a prolonged period during an outbreak [14], and can develop clinical infection or transmit the organism to others, has led to attempts to clear gastrointestinal carriage. O'Donovan et al. found that oral bacitracin eradicated carriage in 2/8 patients, while oral vancomycin cleared colonization in 8/19 [29]. Although oral vancomycin has been found to achieve levels of >1000 mg/kg in feces in patients with *Clostridium difficile* colonization or infection [11–13], lower levels, which may not reliably inhibit enterococci of the VanA or VanB phenotypes, have also been reported [30]. Novobiocin plus tetracycline has been found to be ineffective for clearing GRE colonization and poorly tolerated [31]. The strategy of trying to eradicate colonization with antimicrobial agents (particularly glycopeptides) is likely to be counterproductive by promoting drug resistance. This would be unacceptable.

INFECTION CONTROL MEASURES

Isolation precautions

It is very difficult to eradicate GRE once they become established, and aggressive control measures at an early stage may be justified to limit their spread [5]. In order to prevent transmission in an outbreak setting, nursing patients in single rooms with the use of gloves and gowns (the latter to prevent contamination of healthcare workers from the environment) has been successful [6,14]. Cohorting of nursing staff and patients may also be helpful, but depends upon the provision of adequate staffing numbers [8]. Antiseptic agents have been recommended for handwashing [5], since it has been shown that artificially inoculated *E. faecium* may survive on hands for 30 min and is more effectively removed by using alcoholic chlorhexidine than soap and water [32,33].

In our experience, it has not usually been possible to geographically isolate all colonized patients, due to lack of adequate facilities. We have therefore adopted a risk management approach in deciding which patients should be isolated, concentrating particularly on individuals with diarrhea. Patients with diarrhea are at high risk of disseminating enterococci, causing greater environmental contamination than colonized individuals without diarrhea, potentially providing a reservoir for an outbreak strain of GRE [14,15]. It may be reasonable when isolation facilities are not readily available for a patient with diarrhea but good personal hygiene to be cared for on the main ward rather than isolated in a cubicle without toilet facilities, where there will be increased handling of bedpans and commodes by nursing staff. Conversely, a patient colonized by GRE, but without diarrhea and with poor personal hygiene, may be most appropriately cared for in isolation, if this is available [17].

Transfer of colonized patients between hospitals

Once GRE are established in a hospital, it is easy to see how transfer of resistance genes to other hospitals can occur, either knowingly or unwittingly. Transfer of a colonized patient between two leukemia units in the UK has already been associated with an outbreak at the receiving site [34], and several strains of 'epidemic vancomycin-resistant enterococci' have been described [35]. Infection control teams should notify the receiving hospital on transfer of a patient known to be colonized by GRE. Consideration should also be given to the transfer of GRE-colonized patients from hospitals back into the community. There is growing concern in nursing homes about other resistant bacteria such as methicillin-resistant *S. aureus* and such institutions could also provide a reservoir for GRE [18].

Role of the environment

The role of the inanimate environment in the transmission of enterococci has not been fully elucidated,

but enterococci, including GRE, have been recovered from the environment in several studies [8,14,36,37].

Contamination has been detected in the general environment surrounding patients (e.g. beds) and on medical equipment such as infusion pumps, blood pressure cuffs, stethoscopes and monitoring equipment. Such sites provide the opportunity for spread between patients, either directly, or via attending healthcare workers. We have found contamination of similar sites on our wards. Some sites of contamination, including door and toilet handles, taps and pedal wastebin lids, provide strong indirect evidence of transmission of GRE on hands. Similarly, GRE have been isolated from the hand controls of a portable X-ray machine (C.D. Chadwick, personal communication), the contamination presumably occurring as radiographers moved to and fro between the patient and the machine. Two specific inanimate objects, electronic rectal thermometers [10] and air-fluidized microsphere beds [38], have been epidemiologically implicated in the transmission of *E. faecium*.

The finding of widespread GRE contamination in the environment highlights the need to review cleaning and disinfection practices. Preliminary findings in our own unit show a good correlation between thorough environmental cleaning and a subsequent reduction in the rate of colonization of susceptible patients [16]. Unfortunately, due to staffing shortages and a change in nursing philosophy from task-orientated nursing care (including specific responsibilities for cleaning equipment) to a team-nursing approach (with responsibilities to specific patients rather than tasks), basic ward hygiene and equipment decontamination is being given an increasingly low priority.

Washing and disinfection procedures

Enterococci are hardy bacteria and have long been recognized to be relatively heat tolerant, surviving heat at 60°C for 30 min. It has been suggested that some nosocomial isolates of *E. faecium* may survive at 80°C for 3 min, raising concerns that current washing and disinfection measures in hospitals may be inadequate [39]. However, heat tolerance testing of GRE isolates from Manchester failed to confirm the degree of heat tolerance found by Freeman et al.; we found that although some isolates of glycopeptide-resistant *E. faecium* were able to survive heat at 65°C for 10 min, none survived heat at 71°C [40]. The finding that several isolates survived heat at 65°C for 10 min (viable counts were reduced by <5 $\log_{10}$) raises some concerns about the efficiency of one of the recommended standards for the disinfection of infected linen [41], but it should be stressed that our tests assessed the effect of heat in the absence of a physical washing process. In practice, Wilcox and Jones were unable to demonstrate in situ survival of clinical isolates of enterococci at 71°C for 6 min in a hospital continuous batch tunnel washer [42]. It may be prudent to use a higher (71°C) temperature for the laundry process whenever possible. Providing that current guidelines are followed for bedpan washer-disinfectors [43] and hospital laundry arrangements [41], and so long as equipment is properly maintained [44], these processes should not pose a particular risk for nosocomial transmission of GRE.

CONCLUSION

In order to control GRE, we need to implement the traditional values of good personal hygiene and environmental cleanliness. Sound infection control practices should be reinforced with prudent antibiotic use in all clinical areas. GRE are already draining valuable laboratory and ward resources, in terms of both outbreaks and screening of high-risk patients. They will continue to constitute an important infection control problem for the forseeable future.

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