National guidelines for the judicious use of glycopeptides in Belgium

B. Gordts[1], E. Firre[2], P. Jordens[3], J.-C. Legrand[4], J. Maertens[5] and M. Struelens[6] on behalf of the Infectious Diseases Advisory Board

[1]Departments of Microbiology and Infection Control, AZ St Jan, Brugge, [2]Department of Internal Medicine, CHR La Citadelle, Liège, [3]Department of Pneumology, Onze Lieve Vrouw Ziekenhius, Aalst, [4]Department of Internal Medicine, Centre Hospitalier Universitaire, Charteroi, [5]Department of Hematology, University Hospital, Leuven and [6]Microbiology Laboratory, University Hospital Erasme, Brussels, Belgium

Objective The 'HICPAC guidelines', published in the USA in 1995 stressed the crucial role of restrictive usage of glycopeptides in the strategy to limit the emergence and spread of resistant enterococci. Because controversy still remains in Belgium on the necessity and feasability of restricting glycopeptide usage, the infectious diseases advisory board (IDAB) developed a consensus statement on the judicious use of glycopeptides in Belgium.

Methods The literature on the indications for glycopeptide treatment was reviewed, categorized and discussed by a working party of the IDAB. Consequently, the IDAB reached consensus on the warranted indications for glycopeptide use in Belgium.

Results The opinion of the IDAB-members is reported in a consensus statement specifying the indications for treatment and for prophylaxis with glycopeptide antimicrobials, as well as the situations where glycopeptides should not be used, taking into account the specific epidemiology of bacterial resistance, the availability of antibiotics and the common prescribing practices in Belgium.

Conclusions The IDAB concludes that restrictive usage of glycopeptides must also be a priority in Belgium. Guidelines on the judicious use of these antibiotics adapted to the national situations must contribute to this objective.

Keywords Vancomycin, teicoplanin, glycopeptide, restictive usage, monitoring

Accepted 27 August 2000

Clin Microbiol Infect 2000: 6: 585–592

INTRODUCTION

The glycopeptide antibiotics vancomycin and teicoplanin became the first choice antibiotics to treat severe Gram-positive infections in hospitals, especially as a consequence of the nosocomial pandemic of methicillin-resistant *Staphylococcus aureus* (MRSA). The abundant use of glycopeptides in many hospitals may cause or promote the emergence and spread of resistant pathogens [1] like vancomycin-resistant enterococci (VRE) [2,3], vancomycin- or teicoplanin-resistant *S. aureus* [4–6] *S. epidermidis* [7] and *S. hemolyticus* [8]. In the USA, a consensus paper referred to as 'the HICPAC guidelines', was published in 1995 [9]. This paper proposes a strategy to limit the spread of VRE, consisting of infection control measures, information about the epidemiology of VRE to the hospital staff, and last but not least, a consensus to restrict the use of glycopeptides to essential indications.

Methicillin-resistant strains of staphylococci are endemic nosocomial pathogens. Coagulase-negative staphylococci exhibit β-lactam resistance in 70–80% of the strains from hospitalized patients and co-resistance to aminoglycosides, macrolides-lincosamides and fluoroquinolones is frequent. The prevalence of MRSA infections in many Belgian hospitals increased rapidly during the 1980s: the proportion of MRSA in nosocomial *S. aureus* bacteremia rose from 10% in 1984 to 31% in 1992 [10]. The incidence of MRSA nosocomial acquisition varied widely among acute care hospitals [11]. After implementation of control measures following consensus guidelines published in 1993, the median incidence of MRSA nosocomial acquisition decreased from 3.6 to 1.5 cases/1000 admissions during the period 1994–99 (National MRSA Surveillance Report, 1999). As observed in neighboring coun-

Corresponding author and reprint requests: B. Gordts, Departments of Microbiology and Infection Control, AZ St Jan, Ruddershove, 10, B-8000 Brugge, Belgium
Tel: +32 50 45 26 03
Fax: +32 50 45 26 09
E-mail: bart.gordts@azbrugge.be

tries, widespread clones of MRSA multiresistant to gentamicin, macrolides-lincosamides, rifampin and fluoroquinolones predominated in the 1980s and have progressively been replaced during the 1990s by new epidemic MRSA clones exhibiting less resistance to other classes of antimicrobials (susceptible to gentamicin, macrolides-lincosamides, and rifampin) [12]. Over 95% MRSA strains from Belgium were susceptible to fusidic acid, minocycline and cotrimoxazole.

Although VRE do not yet cause large nosocomial epidemics in Belgium, it has been well documented that asymptomatic carriers of VRE occur in Belgian hospitals and in the community as early as 1993 [13]. Therefore, the increase in glycopeptide use in Belgium [14] is reason for concern. Still, controversy remains on the feasability of restricting glycopeptide usage. In Belgium, the HICPAC guidelines are not generally applied and by many considered too strict. Therefore, the Infectious Diseases Advisory Board (IDAB) re-evaluated the indications for judicious use of glycopeptides in Belgium.

MATERIALS AND METHODS

Based on the HICPAC recommendations, the IDAB studied the literature in order to evaluate for which indications the advantages of glycopeptide treatment outmeasure the disadvantages both for the individual patient and for the population of Belgian patients, taking into account the national situation regarding availability of alternative antibiotics and the prevalence of bacterial resistance to antimicrobials.

The MEDLINE reference database was examined for articles referring to the following keywords: vancomycin, teicoplanin, glycopeptide, monitoring, drug levels, nephrology, posology, peritonitis, CAPD, hemodialysis. The obtained references were examined, categorized and discussed. Consequently the IDAB reached consensus on the warranted indications for glycopeptide use in Belgium, specifying indications for treatment and for prophylaxis, as well as on the situations where glycopeptides should not be used.

RESULTS

Indications for treatment with glycopeptides

Glycopeptides are widely used to treat different categories of infections. The working group reached consensus about the appropriateness of glycopetide treatment for bacteriologically documented or clinically suspected infections as summarized below.

Bacteriologically documented infections

Most penicillin-resistant strains of *S. pneumoniae* in Belgium exhibit a low level of resistance (minimal inhibitory concentration (MIC) 0.12–1.0 mg/L) [15]. Respiratory tract infections therefore can be treated with high dose penicillin. Infection with strains with MIC > 1.0 mg/L can be treated with a third-generation cephalosporin or a carbapenem. *S. pneumoniae* strains with MIC for penicillin > 1 mg/L causing infections of the central nervous system should be treated with meropenem [16].

Methicillin-susceptible *S. aureus* (MSSA) infections should be treated with penicillinase-resistant penicillins and MRSA with glycopeptides. MRSA must be considered to be resistant to all β-lactams (even associated with a β-lactamase inhibitor) and also to carbapenems [17].

Combination of a glycopeptide with rifampin or an aminoglycoside is advocated for MRSA endocarditis, osteoarthritis and severe infection of immunocompromised patients, because of the poor bactericidal activity of glycopeptides [18]. Although no hard data support the clinical relevance of synergy between β-lactams and aminoglycosides or rifampin, most authors recommend combination therapy for staphyloccocal endocarditis and other severe deep-seated staphylococcal infections.

Ampicillin (or ureidopenicillin) remains the treatment of choice for enteroccocal infection in Belgium (associated with an aminoglycoside for endocarditis). Glycopeptides are not indicated unless an ampicillin-resistant enterococcus is considered to be the cause of infection, provided that all pus and all catheters or other foreign bodies are removed from the infection site [19].

Catheters infected by coagulase-negative staphylococci (CNS) in non-neutropenic patients should be removed and not treated with antibiotics. Glycopeptides must be reserved to treat severe CNS infections that also necessitate drainage and/or removal of all foreign devices.

Glycopeptides are never indicated to treat streptococcal infections, except when caused by a rare strain of *viridans streptococcus* with high level resistance to penicillin.

Severe infections due to *C. jeikeium* often occur in cancer patients or in patients with prosthetic devices, particulary cardiac prosthesis. Although most *Corynebacterium* spp. are susceptible to penicillin, *C. jeikeium* infection requires treatment with vancomycin [20].

Empirical treatment of severe infections

The necessity must be stressed for relevant and validated epidemiological data, collected and published on both national and local levels. Based on these reports, the clinician must be able to evaluate the risk that the individual infection is caused by a pathogen resistant to the standard treatment for the given clinical situation. For each empirical treatment this risk should be documented before prescribing glycopeptides.

Infections in the newborn. Glycopeptides are indicated to treat infections related to indwelling catheters in newborns

admitted to an intensive care unit, providing that the causative pathogen is not known. Those infections are frequent, hard to document clinically and bacteriologically, and often caused by methicillin-resistant CNS [21,22].

Burned patients. This type of patient usually suffers from skin and soft-tissue infections, catheter-related infections and pneumonia. Encountered pathogens are *S. aureus, Pseudomonas aeruginosa* and (infrequently) *Enterococcus faecalis* and CNS [23]. Glycopeptides are only indicated if the burned patient is admitted in a unit where the prevalence of MRSA is known to be high.

Clinical sepsis. Empirical treatment with glycopeptides can only be considered when the sepsis is severe, probably catheter-related and when the catheter cannot be removed.

Except in particular epidemiological situations, glycopeptides are never indicated to treat intra-abdominal sepsis empirically, unless β-lactam resistant *Enterococcus* spp. or MRSA were previously isolated from the patient.

Infections in a patient with indwelling percutaneous catheters. The clinical diagnosis of catheter-related sepsis is relatively easy if local inflammation or pus is present. Otherwise, one must rely on the microbiologial (semiquantitative) culture of blood and/or the removed catheter. The treatment of choice is to remove the catheter and to associate or not systemic antibiotherapy. Glycopeptide treatment is indicated for septic unstable patients prior to bacteriogical documentation of the infection and when the catheter cannot be removed [24].

Peri-prosthetic or other foreign body infections. They rarely necessitate empirical antibiotic treatment. For prosthetic valve endocarditis glycopeptides are part of the classical empirical treatment. For natural valve endocarditis, however, glycopeptides are not empirically needed because β-lactam-resistant pathogens are exceptional in this setting.

Meningitis. should not be treated with glycopeptides as long as penicillin-resistance of *S. pneumoniae* (MIC > 1 mg/L) is uncommon.

Meningitis in the presence of a foreign body, an anatomical abnormality or after a previous surgical procedure is often caused by *S. aureus*, enterococci and CNS, but the early differential diagnosis between sterile post-surgical meningitis and bacterial meningitis is cumbersome. In this setting a glycopeptide is indicated when the microscopic examination of the CSF is either inconclusive or shows Gram-positive cocci or when the prevalence of MRSA is high in the hospital unit. A derivative shunt should be removed, or changed and flushed with vancomycin (4–10 mg) [25].

Infections caused by Gram-positive pathogens in patients with severe allergy to β-lactam antibiotics

Patients with suspected IgE-mediated allergy to penicillin need to be assessed by Rast test or cutaneous test. There are no good reliable tests to confirm cephalosporin allergy [26] but cross-allergy with penicillin is rare. Most often in those cases, alternative treatments can be proposed. Infections with *S. pneumoniae* can most often be treated with cephalosporins; *S. pyogenes* with macrolides, *S. aureus* or *Enterococcus* spp. with cotrimoxazole.

In allergic patients, penicillin can sometimes be administred cautiously or, preferrably, a rapid desensitization can be carried out. For patients without bacteriological documentation, we recommend cotrimoxazole, lincosamides or cephalosporins according to the clinical diagnosis.

Treatment of Gram-positive infections caused by penicillin-susceptible pathogens with glycopeptides

In particular circumstances, when the administration of glycopeptides is more convenient, or when the treatment is of long duration and could be continued in the ambulatory setting, teicoplanin intramuscularly could be used instead of another intravenous drug. But these circumstances must be clearly limited to some cases like endocarditis or osteitis.

Antibiotic-associated colitis (AAC) caused by Clostridium difficile

For mild to moderate AAC, the only required treatment is withholding all antibiotics. Treatment with oral metronidazole is indicated if the causative agent cannot be stopped, if fever, leucocytosis or abdominal pain is prominent, when there is peritoneal reaction or in the elderly [27]. This treatment is equivalent to the use of oral vancomycin [28]. Oral vancomycin is only indicated for severe AAC [29,30], and results in improvement in 2 days.

Although metronidazole could be ineffective in some seriously ill or neutropenic patients [31,32] due to its rather poor concentration into the intestinal lumen or to exceptional antimicrobial resistance, it has been advocated as the first choice by the Belgian consensus group [33] for treatment of AAC.

Indications for prophylaxis with glycopeptides

Endocarditis prophylaxis

In 1995 the *European Heart Journal* [34] published a consensus article on antibiotic prophylaxis for infective endocarditis. The only indication for vancomycin in this setting is the high risk patient who has a proven allergy to penicillin.

Surgical prophylaxis in specific situations

The Belgian High Council of Health stated in his recommendations of 1997 that routine use of glycopeptides for prophy-

laxis is not indicated in a hospital solely because of a high incidence of MRSA or MRSE. The prophylactic use of glycopeptides is indicated only for the proven MRSA carrier in whom decontamination has failed or could not be performed. Also, at institutions with a high rate of (postoperative) infections caused by *S. aureus* during an outbreak of MRSA infections, glycopeptides can be used in prophylaxis for major surgical procedures involving implantation of prosthetic material or devices (cardiac and vascular procedures, total hip replacement, ventricular shunts). No data are published concerning the threshold of resistance prevalence that should lead to propylactic use of glycopeptides. More important than the prophylactic use of glycopeptides is to instill appropriate hygiene measures to stop the MRSA epidemic.

Clinical situations where glycopeptides should not be used

Routine prophylaxis

No data support adequately the use of glycopeptides for the prophylaxis of infection or catheter-related sepsis. The best prophylaxis is to use adequate aseptic techniques. Glycopeptides should not be used prophylactically in the neonatal intensive care unit[35–37]. Some limited randomized studies have indeed shown a reduction of CNS septicemia but no reduction in the length of the stay or mortality.

The prophylactic use of glycopeptides is unanimously rejected either for hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) as described in the 1996 version of the 'Advisory Committee on Peritoneal Management of the International Society for Peritoneal Dialysis' [38] (ACPMISPD).

The empirical use of glycopeptides in neutropenic fever

Early studies [39] have advocated that glycopeptides should be administered promptly to treat neutropenic fever, because of the low incidence of treatment failure [40] and the occurrence of lethal Gram-positive superinfections during monotherapy with ceftazidime [41]. However, a retrospective analysis of this 'front-loading' approach demonstrated that in at least 80% of the cases, glycopeptides were given unnecessarily [42]. Numerous large-scale clinical trials have now confirmed that omitting glycopeptides from the early treatment does not adversely affect infectious morbidity and mortality, duration of fever, microbiological efficacy or number of infections, even when inflammation of soft-tissue or catheter exit site is present [43–46]. Since the median time to defervescence in patients receiving adequate antibiotic coverage is 4–5 days, supplementing glycopeptides should not be considered before 96 h of unexplained fever in a clinically stable patient [45] including the bone marrow transplant recipient [46].

When fever persists, no microbial pathogens are identified and no other clinical signs of infection are present, glycopeptides are often added to the initial antimicrobial treatment [46], although it has been demonstrated that this approach offers no benefit [47]. Moreover, the German International Antimicrobial Strategy Study has clearly demonstrated the superiority of supplementing broad-spectrum antifungals over additional (glycopeptide) antibiotics [48]. Therefore, glycopeptides should only be given for FUO in addition to the empirical treatment when the patient's condition is unstable.

Isolation of coagulase-negative staphylococci from a single blood culture

As a rule, one can state that an isolated positive blood culture does not warrant the use of vancomycin or teicoplanin when further blood cultures taken during the same time frame remain negative [49].

Selective digestive decontamination (SDD) and eradication of MRSA colonization

The use of vancomycin has been advocated as part of SDD in hematological or intensive care wards [50]. The benefit of such an attitude is doubtful compared with the risk of selection of resistant strains of enterococci [51] and of bacteremia due to coagulase-negative staphylococci [52].

The use of vancomycin, either systemic or topical, is usually ineffective for decontamination of the patient colonized by MRSA. A better approach is to use intranasal mupirocin and aseptic baths.

Treatment with glycopeptides of infections caused by β-lactam-susceptible Gram-positive microorganisms in patients with renal failure

A single dose of vancomycin every 7 days generally provides a sufficiently high serum level of antibiotic to protect the patient with terminal renal failure against Gram-positive infections. The patient can be treated ambulatory [53], interaction with orally administrated drugs is avoided and the compliance is good. So it is understandable that some nephrologists have reacted vigorously against the HICPAC guidelines and still prescribe glycopeptides to treat infections caused by β-lactam-susceptible pathogens.

The 'ACPMISPD' and others [54] recommends cefazolin or cephalothin + intraperitoneal aminoglycoside [38,55] for the empirical treatment of peritonitis in CAPD. Vancomycin is only indicated for infection due to MRSA or MRSE.

In Europe, most enterococcal strains remain sensitive to ampicillin. In Belgium a recent surveillance study demonstrated that 14.3–66% of patients on chronic hemodialysis are colonized with GRE [56]. Nevertheless, some nephrologic units prescribe vancomycin in empirical treatment of infections when the prevalence of MRSA is high.

In the IDAB's opinion, an hemodialysis unit where MRSA infections are frequent (> 10% of all infections caused by

MRSA) must make every attempt to contain the epidemic in order to enable the first-line use of first-generation cephalosporins instead of glycopeptides. In these wards, the control of patient/staff MRSA nasal carriage is mandatory. The carriers should be treated with mupirocin and cohorted if the treatment is ineffective.

Dosing and monitoring of glycopeptides drug levels

Correct dosing of glycopeptides is critical (Table 1) [57]. Posology for different situations was analyzed from the literature [58–77] and summarized in Table 2.

Systematic monitoring of blood levels during vancomycin treatment was traditionnally recommended [78], but more recently, the usefulness of this practice was repeatedly questionned [59, 79, 80]. It can be concluded that monitoring of vancomycin is useful in the following situations: combination treatment with an aminoglycoside, treatment with a higher dose than usual, when the patient is dialyzed with 'high flux' membranes, in patients with major burns, in intravenous drug addicts or when renal function is rapidly changing [57,78,80]. Serum levels should be determined twice a week and levels of 5–10 mg/L and 2 h peak concentration of 20–40 mg/L are aimed for.

For teicoplanin, contrary to vancomycin, monitoring is not recommended by the manufacturer [73]. However, serum levels should be monitored during treatment of *S. aureus* endocarditis or septic arthritis, where a trough concentration of at least 20 mg/L instead of 10 mg/L is needed. It may also be indicated to determine teicoplanin concentrations in patients with major burns, in intravenous drug addicts or when renal function is rapidly changing.

It is useful to mention that teicoplanin needs a loading dose at the first day of administration.

CONCLUSION

The emergence of resistant Gram-positive microorganisms renders the restriction of glycopeptide usage urgent. Several strategies towards judicious use of these antimicrobial agents

Table 1 Recommended dosage of vancomycin and teicoplanin in different clinical situations

Clinical situation	Vancomycin	Teicoplanin
1 General rules		
Loading dose	15 mg/kg	6 or 12[a] mg/kg 3 times
Next doses	15 mg/kg	6 or 12[a] mg/kg
Interval between doses		
GFR > 90	12 h	24 h
GFR = 50–90	12–24 h	24 h
GFR = 10–50	24–96 h	48 h
GFR < 10	96–168 h	72 h
2 Hemodialysis	15 mg/kg/week[b]	12 mg/kg as loading dose then 6 mg/kg at day 2 and day 3[c] then 6 mg/kg/week
3 CAPD peritonitis	IV: 15 mg/kg/week IP: 30 mg/kg/week	IV: cf posology GFR < 10 IP: 1st week 20 mg/L in each bag 2nd week 20 mg/kg every other bag 3rd week 20 mg/kg in the night bag
4 CAVH(D)-CVVH(D)	cf GFR 10–50 mL/min	cf GFR 10–50 mL/min
5 Neonatology		
Age, weight		
0–7 days, > 1200 g	30 mg/kg/12 h	Not indicated
0–7 days, < 1200 g	15 mg/kg/12 h	Not indicated
8 – 28 days, > 1200 g	45 mg/kg/08 h	Not indicated
8–28 days, < 1200 g	15 mg/kg/24 h	Not indicated
6 Pediatrics		
Interval between doses	40 mg/kg/24 h	3 loading doses at 10 mg/kg every 12 h then 6–10 mg/kg/24 h

[a]In case of *S. aureus* endocarditis or septic arthritis; [b]monitoring needed mainly if high flux membranes are used; [c]D2, D3, D5, D12, D17 in case of *S. aureus* endocarditis; IV: intravenous; IP: intraperitoneal.

Table 2 Clinical situations where glycopeptides are indicated

Clinical situation	Glycopeptide indicated:
Pathogen identified as:	
S. pneumoniae	IgE-mediated allergy to penicillin
S. aureus	Serious infection caused by methicillin-resistant strain
Enterococcus spp.	Serious infection caused by ampicillin-resistant strain
Coagulase-neg. *Staphylococcus* spp.	Serious infection caused by methicillin-resistant strain
Empirical treatment	
Newborn in intensive care unit	Suspected sepsis caused by coagulase-negative *Staphylococcus* spp. and high prevalence of methicillin-resistance, or intubated patient, or presence of intravascular line
Burned patient	Only when prevalence of methicillin-resistance is high among *S. aureus*
Sepsis	Only when related to catheter that cannot be removed and while awaiting microbiology reports
Serious intra-abdominal infection	Only when patient recently carried ampicillin-resistant *Enterococcus* spp. or methicillin-resistant *S. aureus*
Infection of orthopedic or vacular implant	Only when prevalence of methicillin-resistance is high among *S. aureus*
Endocarditis	Infected artificial heart valve
Meningitis	When related to implant, malformation, or recent neurosurgical procedure and Gram-positive cocci present in microscopic examination of cerebrospinal fluid
β-lactam allergy	IgE-mediated allergy to penicillin AND proven Gram-positive infection
Antibiotic-associated colitis	Life-threathening infection
Prophylaxis	
Endocarditis	When prophylaxis with antimicrobials is indicated and risk category is high AND IgE-mediated allergy to penicillin
Surgery	Cardiovascular surgery and IgE-mediated allergy to penicillin
Ventricular shunt	Administered by installation

have been proposed internationally, but are not generally implemented in Belgium. The IDAB proposes these guidelines to the Belgian prescribers based on literature review and consensus panel discussions. The detailed document has been propagated among hospital physicians and pharmacists, and can be used to set up local projects on evaluation of glycopeptide utilization.

ACKNOWLEDGMENTS

The Infectious Diseases Advisory Board comprises: A. Bosly, Yvoir; M. Delmée, Bruxelles; E. Firre, Liège; PF. Laterre, Bruxelles; JC. Legrand, Charleroi; Y. Sibille, Yvoir; M. Struelens, Bruxelles; Y. Van Laethem, Bruxelles; F. Colardyn, Gent; H. Goossens, Edegem; B. Gordts, Brugge; P. Jordens, Aalst; J. Maertens, Leuven; W. Peetermans, Leuven; Y. Valcke, Sint Niklaas; J. Van Eldere, Leuven; W. Vincken, Brussel; D. Vogelaers, Gent.

Our special thanks go to Ms. E. Van Brackel (GlaxoWellcome, Brussels, Belgium) for professional logistic support.

REFERENCES

1. Courcol RJ, Pinkas GR, Martin GR. A seven-year survey of antibiotic susceptibility and its relationship with usage. *J Antimicrob Chemother* 1989; 23: 441–51.
2. Leclercq R, Derlot E, Duval J, Courvalin P 1988 Plasmid mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. *N Engl J Med*; 319: 157–61.
3. Nosocomial enterococci resistant to vancomycin United States 1989–1993. *MMWR Morb Mortal Wkly Rep* 1993; 42: 597–9.
4. Van Eldere J, Hoefnagels-Schuermans A, Peetermans WE, Van Lierde S, Verwaest C. Nosocomial transmission of a methicillin-resistant *Staphylococcus aureus* strain with reduced teicoplanin susceptibility. *Abstracts of the 37th Interscience Conference on Antimicrob Agents and Chemotherapy.* American Society for Microbiology: Washington DC. Abstract J 122.
5. Kaatz GW, Seo SM, Dorman NJ, Lerner SA. Emergence of teicoplanin resistance during therapy of *Staphylococcus aureus* endocarditis. *J Infect Dis* 1990; 162: 103–8.
6. Denis O, Nonhoff C, Byl B, Knoop C, Struelens MJ. Emergence of vancomycin intermediate *Staphylococcus aureus* (VISA) in patients with methicillin resistance *S. aureus* (MRSA) infection in a Belgian hospital. *Abstracts of the 10th European Congress of Clinical Microbiology and Infectious Diseases 2000.* 2000: Abstract 938.

7. O'Connell B, Browne PV, Cefferkey MT, McCann SR. Coagulase negative Staphylococcal bacteremia treated with teicoplanin. *J Antimicrob Chemother* 1993; 31: 438–9.
8. Biavasco F, Giovanetti E, Montanari MP *et al.* Development of resistance to glycopeptide antibiotics: assessment in staphylococci of different species. *J Antimicrob Chemother* 1991; 27: 71–9.
9. Recommendations for preventing the spread of vancomycin resistance. Hospital Infection Control Practices Advisory Committee (HICPAC) *Infect Control Hosp Epidemiol* 1995; 16: 105–13.
10. Struelens MJ. Can we control the rise of methicillin-resistant *Staphylococcus aureus*? *Acta Clinica Belgica* 1994; 49: 63–7.
11. Struelens MJ, Ronveaux O, Jans B, Mertens R, the GDEPIH-GOS-PIZ. Methicillin-resistant *Staphylococcus aureus* epidemiology and control in Belgian hospitals: 1991–95. *Infect Control Hosp Epidemiol* 1996; 17: 503–8.
12. Deplano A, Witte W, Van Leeuwen WJ, Brun and Struelens MJ. Clonal dissemination of epidemic methicillin-resistant *Staphylococcus aureus* in Belgium and neighbouring countries. *Clin Microbiol Infect* 2000; 5: 239–45.
13. Gordts B, Van Landuyt H, Ieven M, Vandamme P, Gooossens H. Vancomycin-resistant enterococci colonising the intestinal tract of hospitalized patients. *J Clin Microbiol* 1995; 33: 2842–6.
14. Gordts B, Van Landuyt H, Hindryckx M. Het antibioticumvoorschrift binnen het ziekenhuis. *Tijdschrift Vóor Geneeskunde* 1997; 53 (1): 40–5.
15. Verhaegen J, Van de Ven N, Verbiest J, Van Eldere J, Verbist L. Evolution of *Streptococcus pneumoniae* serotypes and antibiotic resistance in Belgium – update 1994–98. *Clin Microbiol Infect* 2000; 6: 308–15.
16. Bradley JS, Scheld WR. The challenge of penicillin-resistant *Streptococcus pneumoniae* meningitis: current antibiotic therapy in the 1990s. *Clin Infect Dis* 1997; 24S2: 213–231.
17. Lowny FD. *Staphylococcus aureus* infections. *N Engl J Med* 1998; 338: 520–32.
18. Wilson WR, Karchnen AW, Dajani AC *et al.* Antibiotic treatment of adults with infective endocartitis due to streptococci, enterococci, staphylococci and HACEK microorganisms. *Jama* 1995; 274: 1706–13.
19. Nichols RL, Muzik AC. Enterococcal infection in surgical patients: the mystery continues. *Clin Infect Dis* 1992; 15: 72–6.
20. Brown AE. Other Corynebacteriua and Rhodococcus. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. New York: Churchill Livingstone, 1995: 1872–9.
21. Schmidt BK, Kirpalini H, Corey M *et al.* Coagulase negative staphylococci as true pathogens in new born infants: a cohort study. *Pediatri Infect Dis J* 1987; 6: 1026–31.
22. Schito GC, Pesce A, Debbia EA. Epidemiology of gram positive pathogens in peditrics patients and implications for therapy. *Pediatr Infect Dis J* 1993; 12: 54–6.
23. Signorini M, Grappolini S, Madciano E, Donati L. Updated evaluation of the ativity of antibiotics in a burn center. *Burns* 1992; 18: 500–3.
24. Threlkeld MG, Cobbs CG. Infectious disorders of prosthetic valves and intravascular devices. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. New York: Churchill Livingstone, 1995: 783–92.
25. Boaz JC. Cerebrospinal fluid shunt infections. In: Roos KL, ed. *Central Nervous System Infectious Diseases and Therapy*. New York: Marcel Dekker Inc., 1997: 519–44.
26. Anne S, Reisman R. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995; 74 (2): 167–70.
27. Fekety R, Shah AB. Diagnosis and treatment of *C. difficile* colitis. *JAMA* 1993; 269: 71–5.
28. Johnson S, Homann SR, Bettin KM *et al.* Treatment of asymptomatic *C. difficile* carriers with vancomycin or metronidazole. *Ann Intern Med* 1992; 117: 297–302.
29. Silva JDH, Batts DH, Fekety R. Treatment of *C. difficile* colitis and diarrhea wuith vancomycin. *Am J Med* 1981; 71: 815–22.
30. Fekety R, Silva J, Kaufmann C. Treatment of *C. difficile* antibiotic associated with oral vancomycin. *Am J Med* 1981; 86: 15–9.
31. Rampling A, Warren RE, Berry PJ *et al.* Atypical *C. difficile* colitis in neutropenic patients. *Lancet* 1982; 2: 162–3.
32. Teasly DG, Gerding DN, Olson MN *et al.* Prospective randomized trial of metronidazole vs vancomycin for the treatment of *Clostridium difficile* associated diarrhea and colitis. *Lancet* 1983; 2: 1043–6.
33. Delmée M, Melin P, Peetermans W, Verbist L, Verschraegen G. Treatment of *Clostridium difficile* colitis. Summary of a round table held in Brussels on March 3rd. *Acta Clin Belg 1995* 1994; 50 (2): 114–6.
34. Leport C, Horstkotte D, Burckhardt D. Antibiotic profylaxis for infective endocarditis from an international group of experts towards a European consensus. Group of Experts of the International Society for Chemotherapy. *Eur Heart J* 1995; 16 (Suppl. B): 126–31.
35. Moller JC, Nachtrodt G, Tegtmeyer FK *et al.* Prophylactic low dose vancomycin treatment in very low birth weight infants. *Dev Pharmacol Ther* 1992; 19: 178–82.
36. Spafford PS, Sinkin RA, Cox C *et al.* Prevention of central venous katheter related coagulase negative staphylococcal sepsis in neonates. *J Pediatr* 1994; 125: 259–63.
37. Kacica MA, Horgan MJ, Ochoa L. Prevention of Gram-positive sepsis in neonates weighing less than 1500 grams. *J Pediatr* 1994; 125: 253–8.
38. Keane WF, Alexander SR, Bailie GR *et al.* Peritoneal dialysis related peritonitis treatment recommendations. 1996 update (see comments). *Perit Dial Int* 1996; 16: 557–73.
39. Kramer BS, Ramphal R, Rand KH. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamycin-carbenicillin in febrile granulocytopenic cancer patients. *Antimicrob Agents Chemother* 1986; 30: 64–8.
40. Karp JE, Dick JD, Angelopulos C *et al.* Empiric use of vancomycin during prolonged treatment-induced granulocytopenia: randomised, double-blind, placebo-controlled clinical trial in patients with acute leukemia. *Am J Med* 1986; 81: 237–42.
41. Ramphal R, Kramer BS, Rand KH, Weiner RS, Shands JW. Early results of a comparative trial of ceftazidime versus cephalothin, carbenicillin, and gentamycin in the treatment of febrile granulocytopenic patients. *J Antimicrob Chemother* 1983; 12 (Suppl. A): 81–8.
42. Rubin M, Hathorn JW, Marshall J *et al.* Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med* 1988; 108: 30–5.
43. EORTC. and National Cancer Institute of Canada. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic patients. *J Infect Dis* 1991; 163: 951–8.
44. Novàkovà IRO, Donnelly JP, De Pauw BE. Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. *Antimicrob Agents Chemother* 1991; 35: 672–8.
45. Ramphal R, Bolger M, Oblon DJ *et al.* Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. *Antimicrob Agents Chemother* 1992; 36: 1062–7.

46. Dompeling EC, Donnelly JP, Deresinski SC *et al.* Early identification of neutropenic patients at risk of Gram-positive bacteraemia and the impact of empirical administration of vancomycin. *Eur J Cancer* 1996; 34A: 1332–9.
47. Erjavec Z, de Vries-Hospers HG, Van Kamp H *et al.* A prospective, randomised, double-blind, placebo-controlled trial of teicoplanin in neutropenic patients with persistent fever after imipenem monotherapy. *The tenth International Symposium on Infections in the Immunocompromised Host.* Davos, June 1998: (abstract 013).
48. Link H, Maschmeyer G, Meyer P *et al.* Interventional antimicrobial therapy in febrile neutropenic patients. *Ann Hematol* 1994; 69: 231–43.
49. Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilisation. The true consequences of false positive results. *JAMA* 1991; 265: 365–9.
50. Sanchez M, Mir N, Canton R, Luque R, Lopez B, Baquero F. The effect of topical vancomycin on acquisition, carriage, and infection with methicillin-resistant *Staphylococcus aureus* in critically ill patients. In: *Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy.* American Society for Microbiology: Washington DC, 1997: Abstract J 119.
51. Van der Auwera P, Pensart N, Korten V, Murray BE, Leclercq R. Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide resistant enterococci. *J Infect Dis* 1996; 173: 1129–36.
52. Wade JC, Schimpff SC, Newman KA *et al.* Staphylococcus epidermidis: an increasing cause of infection in patients with granulocytopenia. *Ann Intern Med* 1982; 97: 503–8.
53. Golper TA, Tranaeus A. Vancomycin revisited. *Perit Dial Int* 1996; 16: 116–7.
54. Kuypers D, Vanwalleghem J, Maes B *et al.* Cefazolin serum concentrations with fixed intravenous dosing in patients on chronic hemodialysis treatment. *Nephrol Dial Transplant* 1999; 14: 2050–1.
55. Keane WF, Everett ED, Golper TA *et al.* Peritoneal dialysis related peritonitis treatment recommendations 1993 update. The Ad Hoc Advisory Committee on Peritonitis Management. International Society for Peritoneal Dialysis. *Perit Dial Int* 1993; 13: 14–28.
56. Descheemaeker P, Ieven M, Chapelle S *et al.* Prevalence and molecular epidemiology of glycopeptide resistant enterococci in Belgian renal dialysis units. *J Infect Dis* 1999; 181: 235–41.
57. Leader WG, Chandler Castigliam MH. Pharmacokinetic optimisation of vancomycin therapy. *Clin Pharmacokinet* 1995; 28: 327–42.
58. Sanford JP, Gilbert DN, Moellering RC, Sande MA, eds. *The Sanford Guide to Antimicrobial Therapy.* Antimicrobial Therapy Inc., Hyde Park, Vermont, 1997.
59. Cantu TG, Yamanaka Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis* 1994; 18: 533–43.
60. Quale JMO, Halloran JJ, Devincenzo N *et al.* Removal of vancomycin by high flux hemodialysis membranes. *Antimicrob Agents Chemother* 1992; 36: 1424–6.
61. Bohler J, Reetze Bonorden P, Keller E *et al.* Rebound of plasma vancomycin levels after haemodialysis with highly permeable membranes. *Eur J Clin Pharmacol* 1992; 42: 635–9.
62. Lanese DM, Alfrey PS, Molitoris BA. Markedly increased clearance of vancomycin during hemodialysis using polysulfone dialyzers. *Kidney Int* 1989; 35: 1409–12.
63. Matzke GRO, Connell MB, Collins AJ *et al.* Disposition of vancomycin during hemofiltration. *Clin Pharmacol Ther* 1986; 40: 425–30.
64. Neville LD, Baillard Brumfitt RA, Hamilton J. Efficacy and safety of teicoplanin in Gram positive peritonitis in patients on peritoneal dialysis. *J Antimicrobial Chemotherapy* 1988; 21 (Suppl. A): 123–31.
65. Davies SP, Azadian Kox BS, Brown WJ, Ti EA. Pharmacokinetics of ciprofloxacin and vancomycin in patients with acute renal failure treated by continuous haemodialysis. *Nephrol Dial Transplant* 1992; 7: 848–54.
66. Moellering RC Jr, Krogstad DJ, Greenblatt DJ. Vancomycin therapy in patients with impaired renal function: a nomogram for dosage. *Ann Intern Med* 1981; 94: 343–6.
67. Matzke GR, Mcgory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984; 25: 433–7.
68. Lake KD, Peterson CDA. simplified dosing method for initiating vancomycin therapy. *Pharmacotherapy* 1985; 5: 340–4.
69. Gross JR, Kaplan SL, Kramer WG, Mason EO Jr. Vancomycin pharmacokinetics in premature infants. *Pediatr Pharmacol (New York)* 1985; 5: 17–22.
70. James JK, Palmer SM, Levine DP, Rybak MJ. Comparison of conventional dosing versus continuous infusion vancomycin therapy for patients with suspected or documented gram positive infections. *Antimicrob Agents Chemother* 1996; 40: 696–700.
71. Wilson AP, Gruneberg RN, Neu H. Dosage recommendations for teicoplanin. *J Antimicrob Chemother* 1993; 32: 792–6.
72. Spencer CM, Bryson HM. Teicoplanin: a pharmacoeconomic evaluation of its use in the treatment of Gram positive infecties. *Pharmacoeconomics* 1995; 7 (4): 355–74.
73. Brogden RN, Peters Teicoplanin DH. A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy *Drugs* 1994; 47: 823–54.
74. Graninger W, Wenisch C, Wiesinger E *et al.* Experience with outpatient intravenous teicoplanin therapy for chronic osteomyelitis. *Eur J Clin Microbiol Infect Dis* 1995; 14: 643–7.
75. Chow AW, Azar RM. Glycopeptides and nephrotoxicity. *Intensive Care Medicine* 1994; 20: S23–9.
76. Hoffler D, Koeppe P, Naumann E *et al.* Pharmacokinetics of teicoplanin in hemodialysis patients. *Infection* 1991; 19: 324–7.
77. Beckers B, Brodersen HP, Stolpmannr M *et al.* Efficacy and pharmacokinetics of teicoplanin in hemodialysis patients. *Infection* 1993; 21: 71–4.
78. Prika RD. Vancomycin serum concentration monitoring: a continuate debate. *The Ann Pharmacotherapy* 1994; 28: 1397–9.
79. Catchpole C, Hasting JGM. Measuring pre and post dose vancomycin level time for a change? *Med Microbiol* 1995; 45: 309–11.
80. Moellering RC Jr, Editorial. Monitoring serum vancomycin levels: climbing the mountain because it is there? *Clin infect Dis* 1994; 18: 544–6.