Vancomycin: continuously used, intermittently debated

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Vancomycin has been one of the more commonly used antibiotics in the hospital setting since its introduction into clinical practice during the 1950s. Yet it is not unusual to see a variety of "appropriate" initial and maintenance vancomycin dosing protocols, target concentration ranges and therapeutic drug monitoring strategies across different institutions. The latest controversy over vancomycin use is whether or not vancomycin should be dosed as a continuous infusion (CI) rather than the traditional intermittent dosing (ID) regimen.

Pharmacodynamic predictors of efficacy for vancomycin
Vancomycin and beta-lactams are both best pharmacodynamically described as time-dependent killers. This means that the killing efficiency of these agents is highly correlated with the duration of bacterial exposure to the antibiotic, rather than being correlated to large increases in concentration. Bacterial kill for vancomycin and beta-lactams is maximal at concentrations approximately 4-5 times the MIC. However, vancomycin is different to the beta-lactams in that it also exhibits a prolonged persistent effect ("post-antibiotic effect", PAE). It is for this reason that the area under the concentration time curve to MIC ratio (AUC/MIC ratio) can also be correlated with vancomycin efficacy.

For antibiotics exhibiting time-dependent actions, maximising the time that the antibiotic concentration exceeds the level of the minimum inhibitory concentration (MIC) of the infecting organism is critical to optimise antibiotic dosage. For a short half-life, time-dependent killer without appreciable PAE (e.g. benzylpenicillin), continuous infusion represents the optimal dosing regimen. If the elimination half-life is longer (e.g. ceftriaxone) the prolonged serum concentrations (in conjunction with the increased potency of ceftriaxone, giving generally lower MIC values for most organisms) allow for intermittent administration with the concentration of antibiotic remaining above the MIC for much of the dosing interval.

For vancomycin, the presence of significant PAEs in conjunction with its pharmacokinetic property of a longer elimination half-life (6 hours with normal renal function) make it difficult to rationalise on pharmacodynamic grounds that a continuous infusion regimen should be any more efficacious than intermittent dosing. The persistent effects and prolonged half-life of vancomycin

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Antimicrobials 2003 Travel Awards
Travel awards are available for ASA members presenting research work at the conference. The awards consist of return economy class airfare to Melbourne, accommodation and conference registration. Please indicate that you are applying for a travel award when submitting your conference abstract.

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makes it ideal for dosing at intervals of 12 or 24 hours in patients with normal renal function.

Studies of continuous infusion versus intermittent vancomycin dosing regimens

No in vitro, animal or human study has shown that CI dosing is more effective than ID dosing. For example, in an in vitro model of MRSA infected fibrin platelet clots, simulated vancomycin monotherapy regimens for once daily, twice daily and CI dosing resulted in similar bacterial kill regardless of dosing frequency, and the best regimen was vancomycin once daily (with gentamicin). The pharmacodynamics of CI (500mg loading dose and 2g/24h CI, target steady state concentration of 15mg/L) and ID (1g q12h) vancomycin against two clinical Staphylococcus isolates were compared in ten patients in a prospective randomized crossover study. Both regimens produced concentrations that exceeded the MIC for the entire dosing interval and there were no significant differences between any of the other pharmacodynamic measures in the study. At the doses used in this study CI would not be expected to be any more efficacious than ID, given that there were no differences in pharmacodynamic indices.

Until recently there have been few prospective clinical trials evaluating vancomycin CI versus ID. Wysocki and colleagues evaluated CI (targeting steady state concentrations of 20 to 25mg/L) versus ID (target trough level of 10 to 15mg/L) in 119 critically ill patients with severe methicillin-resistant staphylococcal infections. They concluded that efficacy and toxicity was comparable in both groups but CI was more cost effective than ID ($321 vs $450) mostly due to lower costs for therapeutic drug monitoring (fewer vancomycin concentrations determined in the CI group). The authors acknowledge that there were inadequacies in the pharmacoeconomic assessment since disposables, nursing time and other expenses were not considered. Another limitation acknowledged by the investigators was that the therapeutic monitoring costs were likely to be higher in the study since the number of samples for therapeutic monitoring taken during the study was greater than the normal standard of care.

Toxicity considerations

Cohen and colleagues, drawing upon the rationale for once-daily (OD) dosing of aminoglycosides, prospectively evaluated the efficacy and toxicity of OD versus twice-daily (BD) dosing of vancomycin in 121 hospitalised patients with severe infection. CI dosing is more frequent dosing (and consider CI to be the extreme of small doses at frequent intervals) is related to vancomycin toxicity in a similar pattern to the aminoglycosides, then theoretically, CI dosing may be more toxic than OD or other intermittent dosing regimes

Additional considerations

Both CI and ID (particularly OD) approaches may be considered advantageous with respect to dosing convenience, an important consideration particularly for hospital-in-the-home arrangements where dosage frequency is of great concern. Other factors known to influence vancomycin pharmacodynamics should also be considered. “Local” conditions at the infection site can modify the activity of vancomycin; taking the example of infected biomedical devices where organisms may form biofilm structures, the penetration of vancomycin (like other antibiotics) may be limited and anaerobic conditions may exist which reduce the effectiveness of vancomycin. The growth rate of the organism in the biofilm form may be significantly slower than normal, and it should be noted that in vitro studies with Staphylococcus epidermidis have shown the PAE of vancomycin to be virtually non-existent against non-growing cells. It is unknown how such phenomena may impact on the efficacy of CI or ID approaches.

In summary, the debate over alternative administration regimes of vancomycin cannot be resolved with the current body of evidence. The available information does not suggest any therapeutic advantage for CI versus ID vancomycin, although there may be an economic argument for CI dosing (although this remains to be conclusively demonstrated).

ASA Hospital Antibiotic Usage Survey reminder

ASA is conducting its third Antibiotic Usage Survey in major hospitals around Australia, following previous surveys in 1986 and 1992. Survey forms were sent to Chief Pharmacists, Infectious Disease Physicians and / or Clinical Microbiologists in major hospitals around the country in January 2002 and were resent to those who did not reply in August 2002. Thank you to the 31 hospitals that have returned completed the 2-page survey forms. Unfortunately, 18 hospitals have still not replied to date. Could any ASA members on staff at these hospitals please ensure they do so! Data cannot be analysed until most of these hospitals return completed surveys. Please contact Dr Mike Whitby (phone 07 3240 2595) if you need another survey form. This is a list of the hospitals that were sent the survey. Hospitals that have not yet returned the survey appear in bold typeface.

ACT
• The Canberra Hospital
• Monash Medical Centre
• Royal Children’s Hospital
• Royal North Shore Hospital

NSW
• Westmead Hospital
• Royal Prince Alfred Hospital
• Concord Repatriation General Hospital
• Wollongong & Port Kembla Hospital

VIC:
• Alfred Hospital
• Monash Medical Centre
• Royal Children’s Hospital

Western Hospital

Box Hill Hospital

Geelong Hospital

Royal Melbourne Hospital

St Vincent’s Hospital

Auckland & Repatriation Medical Centre

QLD:
• Toowoomba Hospital
• Rockhampton Hospital

SA:
• The Queen Elizabeth Hospital
• Repatriation General Hospital
• Royal Adelaide Hospital

WA:
• Royal Perth Hospital
• Princess Margaret Hospital for Children
• Sir Charles Gardiner Hospital

TAS:
• Royal Hobart Hospital
• Launceston Public Hospital

NT:
• Royal Darwin Hospital

The pharmacokinetics should also be considered. "Local" conditions at the infection site can modify the activity of vancomycin; taking the example of infected biomedical devices where organisms may form biofilm structures, the penetration of vancomycin (like other antibiotics) may be limited and anaerobic conditions may exist which reduce the effectiveness of vancomycin. The growth rate of the organism in the biofilm form may be significantly slower than normal, and it should be noted that in vitro studies with Staphylococcus epidermidis have shown the PAE of vancomycin to be virtually non-existent against non-growing cells. It is unknown how such phenomena may impact on the efficacy of CI or ID approaches.

In summary, the debate over alternative administration regimes of vancomycin cannot be resolved with the current body of evidence. The available information does not suggest any therapeutic advantage for CI versus ID vancomycin, although there may be an economic argument for CI dosing (although this remains to be conclusively demonstrated).
The Sep 2002 ASA newsletter included a photograph of an amoxicillin Etest MIC on a β-lactamase negative Haemophilus influenzae isolate performed on Haemophilus Test Medium in accordance to the manufacturer’s guidelines. The inoculum was prepared by direct colony suspension of a 20 h culture; viable count was 1 x 10^8 cfu/ml; and the test plate was incubated at 35°C, in 5%CO2, for 20 h.

The questions asked were:
What is the amoxicillin MIC? How should it be reported? Is the appearance of the significant regrowth real? What explanation can be given for this phenomenon?

Unfortunately, we have received no responses to these questions at the time of printing. Readers are invited to email their opinions to the editor on wendy_munckhof@health.qld.gov.au. Answers will be published in the next (March 2003) issue of this newsletter.

Working party on management of staphylococcal sepsis

ASA has set up a working party to write a document entitled “Guidelines for the management of sepsis due to Staphylococcus aureus”.

The staphylococcal working party currently comprises:
- Iain Gosbell (Chairman) (South Western Area Pathology Service, Liverpool, Sydney)
- David Mitchell (Westmead Hospital, Sydney)
- Sally Roberts (LabPlus, Auckland)
- Ben Howden (Austin and Repatriation Medical Centre, Melbourne)
- Wendy Munckhof (Princess Alexandra Hospital, Brisbane)
- Stephen Chambers (Christchurch Hospital)

We plan on writing on the diagnosis and management of:
- Bacteraemia
- Intravenous device infection
- Infective endocarditis
- Septic arthritis and osteomyelitis
- Epidural abscess
- Recurrent boils

We’re about to start planning and writing. If anyone else would like to be involved, email Iain Gosbell at i.gosbell@uws.edu.au now, or forever hold your peace!

References

Are teicoplanin levels important – should we be monitoring them?

George Kotsiou & Clarence Fernandes

Teicoplanin is a glycopeptide antibiotic first described in 1978 and introduced to clinical use in 1988. It is active against Gram-positive bacteria and, like vancomycin, inhibits the transglycosylation reaction in cell wall synthesis. Compared with vancomycin, teicoplanin has a longer serum half life of 88-182 hours and is 90% protein bound. It is not metabolised in the body and nearly all the drug is excreted via the renal route. It is stable in solutions for 48 hrs at room temperature or for 7 days at 4°C and can safely be administered as a bolus intravenously or intramuscularly. As well as its use in critically ill patients, these characteristics apart from its main make teicoplanin well suited for home use in the treatment of osteomyelitis, endocarditis and other infections requiring prolonged parenteral therapy.

Pharmacokinetics and pharmacodynamics of teicoplanin

The pharmacodynamics of the glycopeptides, teicoplanin and vancomycin, are reasonably well known. They do not show concentration dependent killing at therapeutic doses. Available evidence suggests that the duration of teicoplanin concentrations over the mean inhibitory concentration of the pathogen (T>MIC) is the critical pharmacodynamic parameter. However, like vancomycin, there is also evidence of a significant post-antibiotic effect (PAE) for glycopeptides against a range of Gram-positive organisms. At a dose of 6mg/kg/day for 8 days, trough serum concentrations reach 10mg/L, while peaks vary from 20-50mg/L. At a dose of 12mg/kg/day, trough serum concentrations reach 20mg/L by day 3, and peaks between 40 and 100mg/L.

The long half-life of teicoplanin mandates the use of a loading dose to achieve adequate serum levels within an appropriate time period. Trough assays also need to be delayed 3-4 days to ensure steady state has been reached. Current manufacturer’s dosing recommendations for sepsis/bacteraemia, and acute or chronic osteomyelitis state that treatment should commence with a loading dose (400-800mg intravenously 12 hourly for 3 doses) and should be followed by a daily maintenance dose of 400mg. A higher maintenance dose of 12mg/kg/day is recommended for some conditions (acute septic arthritis, Staphylococcus aureus endocarditis). Higher doses may also be required for special patient groups (see below).

Assays used for teicoplanin monitoring

The three major methods available for the assay of teicoplanin in serum and other fluids are high performance liquid chromatography (HPLC), bioassay and fluorescence polarisation immunoassay (FPIA). Teicoplanin is a mixture of six major and four minor components. HPLC methods measure the six major peaks and recovery is calculated as the sum of the six major peaks. Although rapid, the method is difficult and technically demanding and not widely used for this drug. Bioassays provide an accurate method of estimation of teicoplanin levels, but are labour intensive and protocols to overcome interference from other antibacterials have not been clearly established. In

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teicoplanin are hypersensitivity including rash, abnormal liver function tests, fever, local intolerance, diarrhoea, ototoxicity, altered renal function and neuropathy, Staphylococcus aureus endocarditis if low doses of teicoplanin (6mg/kg/day) were used.\textsuperscript{21} Maintaining trough levels above 20mg/L with higher maintenance doses (12mg/kg/day) restored efficacy.\textsuperscript{10} Other trials have demonstrated an association between trough concentration and outcome in endocarditis.\textsuperscript{10,21} These studies form the basis for the current recommendation for an increased maintenance dose in this condition.

A similar requirement for higher dosing of teicoplanin is demonstrated in an unpublished study (protocol 102-012) looking at bone and joint infections.\textsuperscript{19} In this trial patients with acute or chronic osteomyelitis responded equally to both dosing regimens. Other trials have had only small numbers of septic arthritis cases, so this result remains unconfirmed. Despite this, the 12mg/kg/day dose has become the standard dose in the septic arthritis setting because of increased clearance.\textsuperscript{19} This can result in treatment failure and individualisation of dosage regimen is recommended. Similarly, there is evidence that patients with severe burns have increased clearance of many antibiotics. In one study, teicoplanin serum concentrations in burns patients 24 hours after a single dose were half those of healthy adults.\textsuperscript{3,19} In both groups, clearance rates are not only higher but demonstrate a much greater inter-individual variability. In neonates and children, higher doses (up to 30mg/kg/day) may also be considered. Generally results have minimised instances of sub-therapeutic trough levels.\textsuperscript{17}

### Relationship between teicoplanin levels and efficacy and toxicity

The common adverse events with teicoplanin resistance genotypes, when used in a conventional PCR assay system.

Australia the FPIA assay, using reagents concentration is the relevant AstraZenecaTravel Award

We thank AstraZeneca who generously funded the project. Ian Kay of Royal Perth Hospital received the award for his original research, which is summarised below. The award funded Ian's attendance and research presentation at the 43rd Interscience Conference on Antimicrobial Agents and Chemistry (ICAAC) in San Diego USA in 2002. Thanks to AstraZeneca for their generous support.

### Performance of a real-time multiplex PCR assay versus culture for the rapid detection of vanA and vanB genes directly from clinical specimens

Ian Kay, Silvano Palladino, James Flexman, Ingrid Boehm, Anna-Maria Costa, Erica Lambert, & Keryn Christiansen

The emergence and spread of glycopeptide resistance in enterococci has become a significant clinical concern and vancomycin-resistant enterococci (VRE) are now an increasingly important problem in hospitals worldwide. Culture-based detection methods for VRE are typically time-consuming, taking from 2 to 5 days to complete. Current phenotypic methods for the detection of glycopeptide resistant organisms are also limited in their ability to detect low-level glycopeptide resistance, and to distinguish between the different Van types. Many VRE strains have surveillance programs for VRE, however being generally based on culture-based detection methods, they suffer from the inherent limitations of these methods. The advent of real-time PCR technology offers the potential for more rapid confirmation of VRE than is possible with either conventional PCR or phenotypic based methods. In this paper we describe the development and evaluation of a multiplex real-time PCR assay performed on the Roche LightCycler platform, performed directly on rectal swabs and enrichment broths for the detection of VanA and VanB VRE. The primers described in this study have been shown to be highly specific for the detection of the vanA and vanB glycopeptide resistance genotypes, when used in a conventional PCR assay system.\textsuperscript{1} However, the performance of these primers in a real-time PCR format and in conjunction with the novel hybridisation probes for each target has not been previously reported.

### “PCR performance directly on enrichment broths was the most sensitive and rapid method for detection of VRE from rectal swabs”

**Methods**

PCR primers and Fluorescence Resonance Energy Transfer (FRET) hybridisation probes specific for the vanA and vanB genes were designed in a multiplex real-time PCR assay performed directly on faecal material obtained by rectal swabbing and on enrichment broth samples incubated for 24 to 48 hours. DNA was prepared from the rectal swabs and enrichment broths using a commercially available DNA preparation column (QIAGEN QIAamp DNA Stool Mini Kit) designed specifically for use with faecal specimens. One hundred and eighty duplicate rectal swabs were obtained from 42 patients, previously identified as VRE positive and who were being monitored for carriage of VRE. Direct and enrichment broth culture were performed on one swab whilst PCR was performed on the other swab as well as any corresponding presumptive positive enrichment broth.

### Results

In total, 100 specimens from 30 patients remained positive for VRE by at least one method (Table 1). The multiplex real-time PCR assay was positive in 88 enrichment broths from 27 patients, but in only 45 rectal swabs from 15 patients. Direct positive broth culture was performed on only 43 specimens from 11 patients, whilst 75 enrichment broth cultures from 22 patients were positive for VRE. Inhibition studies for the multiplex real-time PCR assay, performed by spiking 50 negative rectal swabs and corresponding enrichment broths with a standard amount of DNA from a vanA Enterococcus faecium, detected inhibition rates of 55.1% and 10% respectively.

### Conclusion

PCR performed directly on enrichment broths was the most sensitive and rapid method for detection of VRE from rectal swabs.

### Table 1: Detection of VRE by real-time PCR and culture

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Total Positive by PCR or culture</th>
<th>Total Positive by culture</th>
<th>VRE Broth PCR positive</th>
<th>VRE broth culture positive</th>
<th>VRE broth culture false positive</th>
<th>VRE broth culture false negative</th>
<th>Direct culture positive</th>
<th>Combined culture positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of positives</td>
<td>n = 100</td>
<td>n = 42</td>
<td>n = 88</td>
<td>n = 15</td>
<td>n = 75</td>
<td>n = 50</td>
<td>n = 43</td>
<td>n = 77</td>
</tr>
<tr>
<td>Total Positive by PCR or culture</td>
<td>100 (100)</td>
<td>30 (100)</td>
<td>88 (88)</td>
<td>27 (90)</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>75 (75)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>VRE Broth PCR positive</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>88 (88)</td>
<td>27 (90)</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>75 (75)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>VRE broth culture positive</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>88 (88)</td>
<td>27 (90)</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>75 (75)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>Direct culture positive</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>88 (88)</td>
<td>27 (90)</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>75 (75)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>Combined culture positive</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>88 (88)</td>
<td>27 (90)</td>
<td>45 (45)</td>
<td>15 (50)</td>
<td>75 (75)</td>
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### Reference

4. ASA Newsletter, December 2002

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AstraZenecaTravel Award

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an amphoterin B, but with fewer adverse events including nephrotoxicity. The pivotal study on which approval as salvage therapy for invasive aspergillosis, teicoplanin in the US and Australia has not been published but appears in the product information and on the FDA site. This was an open label, non-comparative study of caspofungin undertaken in 69 patients with invasive aspergillosis. Of patients evaluable, 84% had refractory disease and 16% were intolerant of other antifungal agents. A favourable outcome was seen in 41% of patients who received at least one dose of caspofungin and 50% of those who received >7 days of therapy. The favourable response rate was 36% in patients refractory to other treatment and 70% in those with toxicity on other therapy.

Although approved for the treatment of invasive aspergillus, no clinical data is based on a single open label non-comparative study. The presence of well documented infection, seriousness of the infection in the patients (pulmonary infection as well as disseminated and CNS infection), the high proportion of patients entering the study due to failure of prior therapy and the presence of 28% of patients who had adjuvance BMT indicate that this study could be extended to one where a lower success rate would be expected. It is not possible to extrapolate the success of this single study in aspergillus to other settings eg fever and neutropenia, although such studies are underway. Further studies must remember the lack of in vitro activity against Cryptococcus, Fusarium and Zygomycetes before extending the caspofungin use to other clinical settings.

Combination therapy

With the availability of antifungal agents acting on different targets in the fungal cell, the possibility of using combination therapy exists. Its role has been explored in difficult to treat infections such as Scedosporium and Aspergillus, as well as Candida and Cryptococcus. However, there is little clinical experience to confirm these in vitro observations apart from case reports.

In vitro testing of Aspergillus species revealed potent synergy with the combination of itraconazole and an allylamine and a triazole. This was most notable with itraconazole and voriconazole. With Scedosporium prolificans, testing revealed synergy between itraconazole and terbinafine in 95% of isolates.

Combinations of caspofungin with fluconazole, 5-flucytosine and amphotericin B have also been tested in vitro. Synergy was noted for these combinations for Cryptococcus neoformans, which is not susceptible to caspofungin alone. Synergy was also noted for amphotericin B and caspofungin against Aspergillus and Cryptococcus. Despite these in vitro findings, there is little clinical experience with combination therapy. The published information from case reports suggests promising benefit.

Conclusion

These new drugs will change our use of antifungal agents. Voriconazole is likely to become the treatment of choice for invasive aspergillus and caspofungin the salvage therapy. However, one should note that both agents are expensive and substantially more so than for other therapies such as conventional amphotericin B. These new drugs will be useful in the treatment of candidiasis with resistance to fluconazole or amphotericin B intolerance. The role of combination therapy will continue to evolve, particularly the combination of voriconazole and terbinafine for the treatment of Scedosporium infections, and the combination of caspofungin, amphotericin B or triazole for the treatment of refractory aspergillosis.

References

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The photographs depicts a combination disc phenotypic test on an isolate of E. coli using NCCLS methodology and based on the original Casal’s test. The plate on the left has a ceftazidime 30 µg disc at 11 o’clock, cefotaxime 30 µg disc at 3 o’clock and a cefpodoxime 10 µg disc at 7 o’clock. The plate on the right has a cefazidime/clavulanate 30/10 µg disc at 11 o’clock, a cefotaxime/clavulanate 30/10 µg disc at 3 o’clock and a cefpodoxime/clavulanate 1/10 µg disc at 7 o’clock.

What is the reason for the difference in zone diameters between antibiotic and antibiotic/ inhibitor combinations?

What is the reason then for the marked variation in this effect between the 3 antibiotic/ inhibitor combinations?

Can you suggest an ESBL family that could be responsible for this phenotype?

Picture quiz provided by Wayne Monaghan, Matthew Sellars and Graeme Nimmo of the Dept. of Microbiology, Princess Alexandra Hospital, Brisbane.

ASA Newsletter, December 2002

7

Quiz: Why is this so?

New antifungal agents

Monica Slavin

Infectious Diseases Physician, Peter MacCallum Cancer Institute & Infection Management Services, Royal Melbourne and Alfred Hospitals

Background

For 30 years, conventional amphotericin B has been the gold standard for treatment of invasive fungal infections due to both yeasts and moulds. Most fungi are susceptible to amphotericin B in vitro, although higher MIC values are found with Trichosporon beigelii, Fusarium spp and the dematiaceous fungi such as Alternaria spp. Pseudallescheria boydii and Scedosporium spp are usually resistant to amphotericin B.1 In many clinical settings, such as invasive aspergillosis in neutropenic or immunosuppressed patients, the response to amphotericin B is poor. This may relate to late diagnosis, host defects or dose-limiting toxicity.

The number of antifungals to choose from is increasing: three lipid formulations of amphotericin B (liposomal amphotericin B, amphotericin B colloidal dispersion and amphotericin B lipid complex), the triazoles (fluconazole, itraconazole and voriconazole) as well as the first licensed echinocandin (caspofungin) are all available. The newest agents, voriconazole and caspofungin, will be discussed.

Triazoles

Voriconazole is the first of the newer triazoles. Others such as posaconazole and ravaconazole are undergoing clinical trials. The advantage of these agents may be activity against Zygomycetes, which until now has been a gap in the triazole spectrum. Voriconazole has activity against yeasts including those intrinsically resistant to fluconazole, such as Aspergillus, Fusarium and importantly Scedosporium spp. and Pseudallescheria boydii, which are often resistant to amphotericin B.2,3 It has no activity against Zygomycetes.4 All the triazoles are associated with similar side effects including abnormal liver function tests, raised bilirubin and rash. Voriconazole has the particular side effect of visual disturbance in up to 30% of recipients. This is transient and may be related to peak levels. Drug interactions are an important consideration. Voriconazole is both a substrate for and inhibitor of CYP2C9 and CYP3C19 enzymes; CYP3A4 is less important. Drugs inducing hepatic enzymes such as rifampicin will increase its metabolism. Voriconazole may compete for metabolism with drugs such as chloramphenicol, tacrolimus, cyclosporine and chemotherapy agents such as vinca alkaloids and cyclophosphamide.

An open label study compared voriconazole primary therapy with voriconazole rather than salvage therapy (61% versus 38%, p=0.02). In the treatment of oesophageal candidiasis, voriconazole was equivalent to fluconazole.5 The overall success rates were 26% with voriconazole and 30.6% with liposomal amphotericin. There were fewer documented breakthrough fungal infections with voriconazole and this benefit was most marked in patients considered as high risk for fungal infection. However, voriconazole did not fulfil the protocol definition of non-inferiority and at any of the other 4 end-points and its role in treatment of febrile neutropenia is not clear, apart from for high risk patients.

Voriconazole has been studied in the treatment of invasive aspergillosis and candidiasis. Herbrecht compared voriconazole with amphotericin B for the treatment of invasive aspergillosis.6 Most patients had undergone allogeneic bone marrow transplantation (BMT), autologous BMT, or were undergoing treatment for haematological malignancy. The primary end-point was response at week 12. Satisfactory outcome occurred in 53% voriconazole and 32% amphotericin B recipients, and survival with voriconazole was 71% versus 58% with amphotericin B. This study suggested outcome was better with voriconazole, rather than amphotericin B. Another open label non-comparative study of efficacy and safety of voriconazole in the treatment of invasive aspergillosis showed overall good responses were seen in 48% of patients.7 Better outcome was seen in those receiving primary therapy with voriconazole rather than salvage therapy (61% versus 38%, p=0.02). In the treatment of oesophageal candidiasis, voriconazole was equivalent to fluconazole.8

Echinocandins

The first of this new class of agents to become available is caspofungin, although micafungin and anidulafungin are undergoing trials. These agents have a different mechanism of action from polyenes and azoles, which act on the ergosterol, synthetic pathway. Echinocandins inhibit the synthesis of an essential component of the fungal cell wall, beta(1,3)-D-glucan. This compound is not present in mammalian cells. Caspofungin has demonstrated most activity in the growing ends of fungal hyphae and has a rapid effect, ceasing growth and replication. A method of antifungal susceptibility testing for this agent against moulds has not yet been established. Caspofungin has activity against Aspergillus and Candida. It does not demonstrate antagonism with amphotericin B. There is increasing exploration of its role in combination therapy. Alone, it does not have activity against Cryptococcus, Fusarium or Zygomycetes.9 It is not recommended for use with concomitant cyclosporin, as three of four healthy subjects who received caspofungin together with cyclosporin developed transient elevations of AST to 2-3 times the upper limit of normal. Caspofungin has thus far been relatively free of side effects although clinical experience is limited.

Only two studies of caspofungin treatment are published, both comparing caspofungin and amphotericin B in the treatment of oesophageal candidiasis in HIV-infected patients. These studies show caspofungin to be as successful in treating oesophageal candidiasis as
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amphotericin B, but with fewer adverse events including nephrotoxicity.4,9 The pivotal study on which approval as salvage treatment for invasive aspergillosis, teicoplanin, was based in the US and Australia has not been published but appears in the product information and on the FHB site. This was an open label, non-comparative study of caspofungin undertaken in 69 patients with invasive aspergillosis. Of patients evaluable, 84% had refractory disease and 16% were intolerant of other antifungal agents. A favourable outcome was seen in 41% of patients who received at least one dose of caspofungin and 50% of those who received >7 days of therapy. The favourable response rate was 36% in patients refractory to other treatment and 70% in those with toxicity on other therapy.

Although approved for the treatment of invasive aspergillosis, caspofungin is based on a single open label non-comparative study. The presence of well documented infection, seriousness of the infection in the patients (pulmonary infection as well as disseminated and CNS infection), the high proportion of patients entering the study due to failure of prior therapy and the presence of 28% of patients who had allogeneic BMT indicate that this study was undertaken in a setting where a low success rate would be expected. It is not possible to extrapolate the success of this single study in aspergillosis to other settings eg fever and neutropenia, although such studies are underway. Further study must remember the lack of in vitro activity against Cryptococcus, Fusarium and Zygomycetes before extending the caspofungin use to other clinical settings.

Combination therapy

With the availability of antifungal agents acting on different targets in the fungal cell, the possibility of using combination therapy exists. Its role has been exploited in difficult to treat infections such as Scedosporium and Aspergillus, as well as Candida and Cryptococcus. However, there is little clinical experience to confirm these in vitro observations apart from case reports.

In vitro testing of Aspergillus species revealed potent synergy with the combination of an allylamine and a triazole.10 There was much more notable with itraconazole and voriconazole. With Scedosporium prolificans, testing revealed synergy between itraconazole and terbinafine in 95% of isolates.11

Combinations of caspofungin with fluconazole, 5-fluorocytosine and amphotericin B have also been tested in vitro. Synergy was noted for these combinations for Cryptococcus neoformans, which is not consitutive to caspofungin alone.12 Synergy was also noted for amphotericin B and caspofungin against Aspergillus and Cryptococcus.13 Despite these in vitro findings, there is little clinical experience with combination therapy synergies followed by other licensed antifungal therapy for primary therapy of invasive aspergillosis. NEJM 2002;347:408-415.

Conclusion

These new drugs will change our use of antifungal agents. Voriconazole is likely to become the treatment of choice for invasive aspergillosis and caspofungin for invasive candidiasis. However, one should note that both agents are expensive and substantially more so than currently available therapies such as conventional amphotericin B. These new drugs will be useful in the treatment of candidiasis with resistance to fluconazole or amphotericin B intolerance. The role of combination therapy will continue to evolve, particularly the combination of voriconazole and terbinafine for the treatment of Scedosporium infections, and the combination of caspofungin, amphotericin B or triazole for the treatment of refractory aspergillosis.

References


teicoplanin are hypersensitivity including rash, abnormal liver function tests, fever, local intolerance, diarrhoea, ototoxicity, altered renal function and serum creatinine. 7,18,19 An association between serum levels and frequency of adverse reactions is uncertain. Most authors feel there is little evidence to support a direct relationship between high trough or peak blood concentrations and most of the known toxicities. However, others have noted higher rates of some reactions with very high doses. 7,18 The development of teicoplanin resistance genotypes, when system.

Australia the FPIA assay, using reagents concentration is the relevant clinical need for teicoplanin levels should be clearly identified in cases where monitoring is being considered.

Clinical situations which may alter teicoplanin clearance

In patients with renal impairment, the total body and renal clearance of teicoplanin decreases significantly. Dosage adjustments can be made based on the ratio of estimated or measured creatinine clearance to normal.7 The effect on teicoplanin clearance of renal replacement therapies such as intermittent haemodialysis, continuous ambulatory peritoneal dialysis (CAPD) and various haemofiltration techniques is more difficult to estimate. Elimination is dependent on multiple factors that vary with the patient and the parameters of the specific technique used. Generally the teicoplanin half life is prolonged and maintenance doses need to be given at intervals of some days. 8,9

Teicoplanin levels, as a routine procedure, is generally not recommended. 8,9 Guidelines have been published defining specific situations in which monitoring might be useful. 8,9 Monitoring to reduce toxicity is more difficult to justify based on current evidence. One would only advocate it in the unusual circumstance of very high dosing being used (>12mg/kg/day). It may also be helpful in patients with renal impairment, to ensure that excessively high trough levels are not maintained for prolonged periods. These patients often have sufficiently unpredictable clearance to justify monitoring as a guide to frequency of dosing in any case.

In this study we have also demonstrated an association between trough concentration and outcome in endocarditis. 20,21 These studies form the basis for the current recommendation for an increased maintenance dose in this condition.

A similar requirement for higher dosing in patients with endocarditis is suggested by results of an unpublished study (protocol 102-012) looking at bone and joint infections. 22 In this trial patients with acute or chronic osteomyelitis responded equally to both dosing regimens. Other trials have had only small numbers of septic arthritis cases, so this result remains unconfirmed. Despite this, the 12mg/kg/day dose has become the standard of care for septic arthritis. Other sites of infection have not been as thoroughly studied. Generally the minimum therapeutic concentrations are well above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored

Relationship between teicoplanin levels and efficacy and toxicity

The common adverse events with teicoplanin are hypersensitivity including rash, abnormal liver function tests, fever, local intolerance, diarrhoea, ototoxicity, altered renal function and serum creatinine. 7,18,19 An association between serum levels and frequency of adverse reactions is uncertain. Most authors feel there is little evidence to support a direct relationship between high trough or peak blood concentrations and most of the known toxicities. However, others have noted higher rates of some reactions with very high doses. 7,18

The pharmacokinetics of teicoplanin are also altered in a number of other conditions. Intravenous drug users with endocarditis often require higher doses because of increased clearance. 8 This can result in treatment failure and individualisation of the dosage regimens is recommended. Similarly, there is evidence that patients with severe burns have increased clearance of many antibiotics. In one study, teicoplanin serum concentrations in burns patients 24 hours after a single dose were half those of healthy adults. 10 In both groups, clearance rates are not only higher but demonstrate a substantial inter-individual variability. In neonates and children, higher doses (up to 30mg/kg/day) may also be selected to maximise the probability of achieving therapeutic trough levels. 11

When to monitor teicoplanin levels?

In summary, teicoplanin serum trough concentration is the relevant pharmacokinetic parameter. There is some data suggesting a modest association between toxicity and serum levels, but this data has not been shown at very high trough levels. There is good data linking efficacy to the serum trough levels and this is particularly true for endocarditis. Furthermore, there are clear, identifiable groups with erratic and unpredictable clearance (both high (IVDU, burns, paediatric patients) and lower clearance (renal impairment, renal replacement therapies)). This data should not be taken as an absolute guide, but suggest a prima facie case in favour of monitoring. However, to be justifiable it is also necessary to demonstrate clinical benefit from monitoring. This has not been formally done for teicoplanin. The many permutations of patient variables, organism and site of infection would seem difficult hurdles to overcome for such a study to proceed.

Monitoring of teicoplanin serum levels, as a routine procedure, is generally not recommended. 8,9 Guidelines have been published defining specific situations in which monitoring might be useful. 8,9 Maintaining adequate trough concentrations for teicoplanin therapy is certainly important, particularly for endocarditis and septic arthritis. This can be confirmed if trough levels are measured, but in most cases using a 12mg/kg/day dose will be sufficient. Perhaps the IVDU, burns and paediatric patients groups are special cases in this regard. For routine patient care, it is unlikely monitoring will alter treatment outcome (once cleared doses are used). Again, the patient groups with variably increased teicoplanin clearance might be an exception.

Monitoring to reduce toxicity is more difficult to justify based on current evidence. One way would only advocate it in the unusual circumstance of very high dosing being used (>12mg/kg/day). It may also be helpful in patients with renal impairment, to ensure that excessively high trough levels are not maintained for prolonged periods. These patients often have sufficiently unpredictable clearance to justify monitoring as a guide to frequency of dosing in any case.

Another argument in favour of monitoring is one of cost. In our experience the minimum therapeutic concentrations are well above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance doses (12mg/kg/day) restored above 20mg/L with higher maintenance
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**Working party on management of staphylococcal sepsis**

ASA has set up a working party to write a document entitled “Guidelines for the management of sepsis due to *Staphylococcus aureus*”.

The staphylococcal working party currently comprises:

- Iain Gosbell (Chairman) (South Western Area Pathology Service, Liverpool, Sydney)
- David Mitchell (Westmead Hospital, Sydney)
- Sally Roberts (LabPlus, Auckland)
- Ben Howden (Austin and Repatriation Medical Centre, Melbourne)
- Wendy Munchkof (Princess Alexandra Hospital, Brisbane)
- Stephen Chambers (Christchurch Hospital)

We plan on writing on the diagnosis and management of:

- Bacteraemia
- Intravenous device infection
- Infective endocarditis
- Septic arthritis and osteomyelitis
- Epidural abscess
- Recurrent boils

We’re about to start planning and writing. If anyone else would like to be involved, email Iain Gosbell at i.gosbell@unsw.edu.au now, or forever hold your peace!

**Are teicoplanin levels important – should we be monitoring them?**

George Kotsiou & Clarence Fernandes

Microbiology Dept, Pacific Laboratory Medicine Services, Royal North Shore Hospital, Sydney

Teicoplanin is a glycopeptide antibiotic first described in 1978 and introduced to clinical use in 1988. It is active against Gram-positive bacteria and, like vancomycin, inhibits the transglycosylation reaction in cell wall synthesis. Compared with vancomycin, teicoplanin has a longer serum half-life of 88-182 hours and is 90% protein bound. It is not metabolised in the body and nearly all the drug is excreted via the renal route. It is stable in solutions for 48 hrs at room temperature or for 7 days at 4°C and can safely be administered as a bolus intravenously or intramuscularly. As well as its use in critically ill patients, these characteristics apart from its main make teicoplanin well suited for home use in the treatment of osteomyelitis, endocarditis and other infections requiring prolonged parenteral therapy.

**Pharmacokinetics and pharmacodynamics of teicoplanin**

The pharmacodynamics of the glycopeptides, teicoplanin and vancomycin, are reasonably well known.1,2 They do not show concentration dependent killing at therapeutic doses. Available evidence suggests that the duration of teicoplanin concentrations over the mean inhibitory concentration of the pathogen (T>MIC) mandates the use of a loading dose to achieve adequate serum levels within an appropriate time period. Trough assays also need to be delayed 3-4 days to ensure steady state has been reached.3

The long half-life of teicoplanin allows a single daily loading dose of 400mg to be administered as a bolus intravenously or intramuscularly. The trough serum concentration range of 10-15mg/L is achieved within 3-4 days. The peak trough ratio of teicoplanin is 20:1. Higher trough levels may be required for special patient groups (see below).

**Assays used for teicoplanin monitoring**

The three major methods available for the assay of teicoplanin in serum and other fluids are high performance liquid chromatography (HPLC), bioassay10 and fluorescence polarization immunoassay (FPIA).1,11 Teicoplanin is a mixture of six major and four minor components. HPLC methods measure the six major peaks and recovery is calculated as the sum of the six major peaks. Although rapid, the method is difficult and technically demanding and not widely used for this drug. Bioassays provide an accurate method of estimation of teicoplanin levels,10,12 but the labour intensive and protocols to overcome interference from other antibacterials have not been clearly established. In
ASA Hospital Antibiotic Usage Survey reminder
ASA is conducting its third Antibiotic Usage Survey in major hospitals around Australia, following previous surveys in 1986 and 1992. Survey forms were sent to Chief Pharmacists, Infectious Disease Physicians and / or Clinical Microbiologists in major hospitals around the country in January 2002 and were resent to those who did not reply in August 2002. Thank you to the 31 hospitals that have returned completed the 2-page survey forms. Unfortunately, 18 hospitals have still not replied to date. Could any ASA members on staff at these hospitals please ensure they do so! Data cannot be analysed until most of these hospitals return completed surveys. Please contact Dr Mike Whitty (phone 07 3240 2595) if you need another survey form. This is a list of the hospitals that were sent the survey. Hospitals that have not yet returned the survey appear in bold typeface.

ACT
- The Canberra Hospital
- Monash Medical Centre
- Royal Children’s Hospital
- Royal Women’s Hospital
- Sir Charles Gardiner Hospital
- Fremantle Hospital

NSW
- Westmead Hospital
- St Vincent’s Hospital
- Prince of Wales Hospital
- St George Hospital
- Nepean Hospital
- Royal Prince Alfred Hospital
- Concord Repatriation General Hospital
- Wollongong & Port Kembla Hospital
- Royal North Shore Hospital
- John Hunter Hospital
- Liverpool Hospital
- New Children’s Hospital Westmead

VIC:
- Alfred Hospital
- Monash Medical Centre
- Royal Children’s Hospital
- Royal Women’s Hospital
- Western Hospital
- Box Hill Hospital
- Geelong Hospital
- Royal Melbourne Hospital
- St Vincent’s Hospital
- Austin & Repatriation Medical Centre

QLD:
- Toowoomba Hospital
- Rockhampton Hospital

SA:
- The Queen Elizabeth Hospital
- Repatriation General Hospital
- Royal Adelaide Hospital
- Women’s and Children’s Hospital
- Flinders Medical Centre
- Modbury Hospital
- Lyell McEwin Health Service

WA:
- Royal Perth Hospital
- Princess Margaret Hospital for Children
- Sir Charles Gardiner Hospital
- Fremantle Hospital

TAS
- Royal Hobart Hospital
- Launceston Public Hospital
- NT
- Royal Darwin Hospital

makes it ideal for dosing at intervals of 12 or 24 hours in patients with normal renal function.

Studies of continuous infusion versus intermittent vancomycin dosing regimens

No in vitro, animal or human study has shown that CI dosing is more effective than ID dosing. For example, in an in vitro model of MRSA infected fibrin platelet clots, simulated vancomycin monotherapy regimens for once daily, twice daily and CI dosing resulted in similar bacterial kill regardless of dosing frequency, and the best regimen was vancomycin once daily (with gentamicin). The pharmacodynamics of CI (500mg loading dose and 2g/24h CI, target steady state concentration of 15mg/L) and ID (1g q12h) vancomycin against two clinical Staphylococcus isolates were compared in ten patients in a prospective randomized crossover study.2 Both regimens produced concentrations that exceeded the MIC for the entire dosing interval and there were no significant differences between any of the other pharmacodynamic measures in the study. At the doses used in this study CI would not be expected to be any more efficacious than ID, given that there were no differences in pharmacodynamic indices.

Until recently there have been few prospective clinical trials evaluating vancomycin CI versus ID. Wysocki and colleagues3 evaluated CI (targeting steady state concentrations of 20 to 25mg/L) versus ID (target trough level of 10 to 15mg/L) in 119 critically ill patients with severe methicillin-resistant Staphylococcal infections. They concluded that efficacy and toxicity was comparable in both groups but CI was more cost effective than ID ($321 vs $450) mostly due to lower costs for therapeutic drug monitoring (fewer vancomycin concentrations determined in the CI group). The authors acknowledge that there were inadequacies in the pharmacoeconomic assessment since disposables, nursing time and other expenses were not considered. Another limitation acknowledged by the investigators was that the therapeutic monitoring costs were likely to be higher in the study since the number of samples for therapeutic monitoring taken during the study was greater than the normal standard of care.

“No in vitro, animal or human study has shown that continuous infusion dosing of vancomycin is more effective than intermittent dosing”

with serum creatinine clearances >50ml/min.4 Although CI regimens were not evaluated and the patient group were not as severely ill as in Wysocki’s study, the efficacy and mean trough concentrations (>10mg/L) in the ID group were not different to the BD group. Of note was a non-significant trend for increased toxicity in the BD group (eg. nearing loss in OD vs BD was 1/31 (3.2%) vs 5/32 (15.6%)) although patients were also receiving unspecified additional antibiotics that may have included aminoglycosides. Associations with vancomycin exposure and toxicity have been debated in the literature for many years, with many challenging that observed toxicity is related to co-administered drugs (eg aminoglycosides), rather than vancomycin itself. On the other hand, if more frequent dosing (and consider CI to be the extreme of small doses at frequent intervals) is related to vancomycin toxicity in a similar pattern to the aminoglycosides, then theoretically, CI dosing may be more toxic than OD or other intermittent dosing regimes

Additional considerations

Both CI and ID (particularly OD) approaches may be considered advantageous with respect to dosing convenience, an important consideration particularly for hospital-in-the-home arrangements where dosage frequency is of great concern. Other factors known to influence vancomycin pharmacodynamics should also be considered. “Local” conditions at the infection site can modify the activity of vancomycin; taking the example of infected biomedical devices where organisms may form biofilm structures, the penetration of vancomycin (like other antibiotics) may be limited5 and anaerobic conditions may exist which reduce the effectiveness of vancomycin.6 The growth rate of the organism in the biofilm may be significantly slower than normal,7 and it should be noted that in vitro studies with Staphylococcus epidermidis have shown the PAE of vancomycin to be virtually non-existent against non-growing cells.8 It is unknown how such phenomena may impact on the efficacy of CI or ID approaches.

In summary, the debate over alternative administration regimes of vancomycin cannot be resolved with the current body of evidence. The available information does not suggest any therapeutic advantage for CI versus ID vancomycin, although there may be an economic argument for CI dosing (although this remains to be conclusively demonstrated).
Plenary Speakers*

• Mark Enright
  Evolution of MRSA
  Senior Research Fellow / Royal Society University Research Fellow, Dept of Biology and Biochemistry, University of Bath, Bath, United Kingdom

Mark is well known for his work on the evolution of MRSA and is a leader in the field of staphylococcal typing, particularly using multilocus sequence typing (MLST). As well as giving this plenary session, he will also be participating in the typing workshop.

• Bart Currie
  Antibiotic prescribing in the “Top End” – why is it different?
  Infectious Diseases Physician, Royal Darwin Hospital, Menzies School of Health Research, Northern Territory

Bart is an infectious diseases physician based in Darwin with many years experience in tropical clinical infectious diseases. He has also published widely in this field and has a particular interest in melioidosis.

* The third international plenary speaker has yet to be confirmed.

Symposia

• Adverse Drug Reactions: Hot Gossip and True Tips
  • Beta-lactams - Hypersensitivity and Serum Sickness and the Fluclacoxillin/Dicloxacillin/ Augmentin Controversy
  • Quinolones: Hypoglycaemia and QT problems
  • Voriconazole and Photosensitivity

• Vancomycin-resistant enterococci
  • Australia: the Complete VRE Alphabet
  • Screening and Laboratory Detection – After the Flood
  • Treatment, Decolonisation and Suppression

• Antifungal agents
  • Antifungal Susceptibility Testing : Routine Laboratory versus Reference Laboratory
  • Trimming away the Fat (Liposomals Exposed)
  • Pharmacoeconomics of the New Antifungals

• Drug Use in Hospitals
  • Drug Approval Software
  • DDD’s (Drugs, Definitions and Doses)
  • Hospital Utilisation Data

• AGAR Staph Awareness Program
  • 15 years of Evolution
  • Community-acquired Staphylococcal Infections
  • Update on VISA and VRSA

• AGAR Streptococcus pneumoniae / Gram Negative Programs
  • Pneumococcal Data
  • Gram-negative Data
  • Proffered Papers

Workshop

• Bacterial Typing

Poster session

Registration and abstract submission


Updated conference and accommodation information will also be on the website.

Dates to remember

Deadline for abstract submission: Friday 21st February 2003
Deadline for early registration: Friday 21st February 2003
Abstract notification: March 2003 (all accepted abstracts will be eligible to register at the early registration price)

Antimicrobials 2003 Travel Awards

Travel awards are available for ASA members presenting research work at the conference. The awards consist of return economy class airfare to Melbourne, accommodation and conference registration. Please indicate that you are applying for a travel award when submitting your conference abstract.

Vancomycin: continuously used, intermittently debated

Michael J Taylor1 & Craig R Rayner2 1Pharmacist & PhD candidate; 2Lecturer, Dept of Pharmacy Practice, Victorian College of Pharmacy, Monash University, Melbourne

Vancomycin has been one of the more commonly used antibiotics in the hospital setting since its introduction into clinical practice during the 1950s, yet it is not unusual to see a variety of “appropriate” initial and maintenance vancomycin dosing protocols, target concentration ranges and therapeutic drug monitoring strategies across different institutions. The latest controversy over vancomycin use is whether or not vancomycin should be dosed as a continuous infusion (CI) rather than the traditional intermittent dosing (ID) regimen.

The suggestion of a CI regimen being “better” may have evolved from the use of this strategy with several of the beta-lactams, and the observations that CI regimens have been demonstrated to be of clinical/economic benefit for these agents. However, there are important pharmacodynamic distinctions between vancomycin and beta-lactams and in the strength of evidence for CI dosing for vancomycin.

Pharmacodynamic predictors of efficacy for vancomycin

Vancomycin and beta-lactams are both best pharmacoodynamically described as time-dependent killers. This means that the killing efficiency of these agents is highly correlated with the duration of bacterial exposure to the antibiotic, rather than being correlated to large increases in concentration. Bacterial kill for vancomycin and beta-lactams is maximal at concentrations approximately 4-5 times the MIC. However, vancomycin is different to the beta-lactams in that it also exhibits a prolonged persistent effect (“post-antibiotic effect”, PAE). It is for this reason that the area under the concentration time curve to MIC ratio (AUC:MIC ratio) can also be correlated with vancomycin efficacy.

For antibiotics exhibiting time-dependent actions, maximising the time that the antibiotic concentration exceeds the level of the minimum inhibitory concentration (MIC) of the infecting organism is critical to optimise antibiotic dosage. For a short half-life, time-dependent killer without appreciable PAE (e.g. benzylpenicillin), continuous infusion represents the optimal dosing regimen. If the elimination half-life is longer (e.g. ceftriaxone) the prolonged serum concentrations (in conjunction with the increased potency of ceftriaxone, giving generally lower MIC values for most organisms) allow for intermittent administration with the concentration of antibiotic remaining above the MIC for much of the dosing interval.

For vancomycin, the presence of significant PAEs in conjunction with its pharmacokinetic property of a longer elimination half-life (6 hours with normal renal function) make it difficult to rationalise on pharmacodynamic grounds that a continuous infusion regimen should be any more efficacious than intermittent dosing. The persistent effects and prolonged half-life of vancomycin

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