

VANCOMYCIN (Comment)

Dosing guidelines in the first year of life

Use in the first three months of life: There have been more than thirty studies of the way that term and the preterm babies 'handle' vancomycin, and many different treatment guidelines currently exist. Some early policies held that treatment should always be guided by the routine assessment of plasma levels (as is still conventional when giving an aminoglycoside). Some also noted how, because renal glomerular filtration is the major factor influencing drug elimination, treatment might usefully be guided by a knowledge of plasma creatinine levels. Fewer seemed to take on board the fact that, because renal excretion has such a major impact on clearance (Schaible *et al.*, 1986; Kildoo *et al.* 1989), postnatal age really has to be taken into account when prescribing this drug in babies less than 10 days old. One little recognised reason is that, because vancomycin is seldom used in babies less than a week old, there is still very little information on clearance in babies as young as this. Others, more recently, have pointed to the way in which the volume of distribution seems to differ in babies with overt patent ductus, and to the fact that clearance is marginally slower in babies who are 'light for dates'. However such precision seems unnecessary now we know that, with any of the currently available commercial products, toxicity is almost never seen even with high dose treatment (Zimmermann, 1995), and that the only important challenge is to ensure an adequate minimal blood level.

The strategy recommended by *NeoFax*[®], perhaps the most widely used American neonatal reference text, currently uses a combination of postmenstrual and postnatal age (see table). This will almost always deliver an adequate minimum trough blood level (>5 mg/l). The one drawback to this policy is that it requires some babies to be treated once every 18 hours, a dosing strategy that all too often results in administrative error.

Vancomycin dosing interval chart (15 mg/kg doses)

Postmenstrual age	Postnatal age	Dose interval
Less than 30 weeks	Less than 15 days	18 hours
"	15 or more days	12 hours
30 to 36 weeks	Less than 15 days	12 hours
"	15 or more days	8 hours
37 to 44 weeks	Less than 8 days	12 hours
"	8 or more days	8 hours
More than 44 weeks	All ages	6 hours

Many early guidelines were based on the premise that it was just as important to avoid a trough level of more than 10 mg/l as a level of less than 5 mg/l. However, in a genuinely septic baby, a sub-therapeutic blood level is much more hazardous than a level that, though higher than is necessary for most infections, is still lower than the trough level now recommended if there is a significant risk that *S aureus* bacteraemia may be developing in a patient with an intravascular line in place (see below). The regimen advocated by this *Formulary* since May 2008 has, therefore, been designed to deliver rather higher trough levels.

Older children: Clearance is certainly higher in young children than it is in adult life, and it is well known that many children over a year old do not achieve a trough plasma level of more than 5 mg/l unless they are given 60 mg/kg a day IV in divided doses once every 6 or 8 hours (Miles *et al.*, 1997; Glover *et al.*, 2000; Zylbersztajn *et al.*, 2008). This is significantly higher than the 40 mg/kg/day dose still currently recommended by the manufacturers. Key American reference texts (Taketomo *et al.*, 2009) which, like the *British National Formulary* and *BNF for children*, still repeat this advice seems to be leaving many children with methicillin-resistant *Staphylococcus aureus* infections sub-optimally treated (Frymoyer *et al.*, 2009).

Treatment by continuous infusion: Some in France have long advocated treatment by continuous infusion instead of intermittent dosing, and Plan *et al.*, 2008 have shown that a dose of 30 mg/kg a day eventually provides most babies of less than 34 weeks gestation with a stable, therapeutic and non-toxic blood level of 10–25 mg/l. Most of the 145 babies in this study were 1–2 weeks old. The authors say that therapeutic levels are achieved so fast that a loading dose is not necessary (quoting a single rather obscure abstract relating to the use of this strategy in much older children [Le Normand *et al.*, 1993]). However that was not the view of those who did both of the earlier studies where *babies* were given a continuous infusion (Borderon *et al.*, 1994; Pawlotsky *et al.*, 1998) and, given the drug's initial long half life (nearly 10 hours in the very preterm baby), there is just no way a therapeutic level can be delivered quickly if a loading dose is not used (Embleton and Berrington, 2009). Even in the study reported by Le Normand in 2–12 year old children (where the half life was 2 hours), plateau levels might only be achieved after 12 hours.

Vancomycin can be given into the same line as parenteral nutrition, but it is incompatible with some drugs, so some care needs to be taken before giving a continuous rather than an intermittent infusion and there is, in any case, no evidence that a continuous infusion is any more effective than intermittent treatment in adults

when treating proven blood born infection (Wysocki *et al.*, 2001). It may, however, be a useful strategy when managing central nervous system infection (Barois *et al.*, 1986) and make direct intrathecal administration unnecessary. The total daily dose used in Plan's study is, it should be noted, in line with what is currently recommend by this *Formulary*.

When considering continuous infusion it should be noted that, according to Trissel's authoritative reference text, while it is safe to give some other antibiotics (such as acyclovir, amikacin, ampicillin, fluconazole, linezolid, meropenem and zidovudine) terminally using a Y-connector into a line that contains vancomycin, it is **not** safe to co-infuse many other antibiotics (including most cephalosporins, chloramphenicol, and several commonly used penicillins). The safety of co-infusion with a wide range of other drugs has never been established. It is certainly **not** safe to give an injection of dexamethasone or phenobarbital into a line containing vancomycin and, although terminal co-infusion with hydrocortisone succinate seems safe, co-infusion with dexamethasone is not.

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Minimising indiscriminate vancomycin use

Most neonatal staphylococcal infection is currently caused by coagulase-negative staphylococci (often caused by colonisation of a long line, endotracheal tube or other invasive piece of plastic) and many of these organisms have now become partially resistant to flucloxacillin. Most of these infections are insidious low grade affairs however, and there is good evidence that flucloxacillin, dicloxacillin and oxacillin, are still bacterostatic even when they are not bactericidal, and that empiric treatment with one of these drugs will at least hold any such infection in check until there is confirmatory evidence that the baby really is infected and what the organism actually is (Karlłowicz *et al.*, 2000; Laurence *et al.*, 2005). Such an approach could greatly reduce the number of babies currently being treated with vancomycin – an approach that must risk speeding the day when vancomycin-resistant organisms start to become commonplace.

A joint working party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association brought out a detailed and well-argued joint report in late 2006 (Gemmell, *et al.*, 2006) reviewing how to prevent and treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and this endorses many of the recommendations made regarding the need to limit the indiscriminate use of the glycopeptides antibiotics (vancomycin and teicoplanin) made in a Belgian report issued six years earlier (Gordts *et al.*, 2000). Their guidelines suggest that empiric treatment with vancomycin or teicoplanin is appropriate where there is evidence of vascular catheter-related sepsis, but (in agreement with the report by Karlłowicz already referred to) it says that this should *not* be used after “the isolation of coagulase-negative staphylococci from a single blood culture”.

The guidelines are quite firm in stating that flucloxacillin “remains the drug of choice for the definitive treatment of methicillin-sensitive *S aureus* [infection] in the UK, and is also preferred for empirical therapy except in situations where methicillin-resistant *S aureus* is highly prevalent.” They are equally firm in advising that “step down therapy to flucloxacillin from glycopeptides and linezolid should be used where possible once the antibiotic susceptibilities of the *S aureus* strain are known”. Convenience, cost, and patient safety all support this recommendation, and relapse is less common when patients infected with a methicillin-sensitive strain are treated with flucloxacillin (Johnson *et al.*, 2003; Fowler *et al.*, 2005).

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Measuring ‘peak’ and ‘trough’ plasma levels

When vancomycin first came into use there was as much concern that over-treatment might cause toxicity, as concern for the risks associated with under-treatment. Now it is clear that toxicity is rare (see below), efficacy rather than safety has become the only good reason for recommending routine monitoring. Indeed, although the *British National Formulary* still gives the impression that monitoring is essential it has, for the last 15 years, become generally accepted that, in the absence of suspected renal failure, routine monitoring is really not necessary (Freeman *et al.*, 1993; Saunders, 1994; Cantú *et al.*, 1994).

Some bacteriologists were also reluctant to stop measuring both peak levels as well as 'trough' levels at first because the measured peak level did not always seem to correlate with what might have been expected from the earlier 'trough' level. It is, however, now generally accepted that minor variations in the exact time over which the drug was infused compounded by variation in the exact time at which the so-called peak level specimen was collected can have a marked impact on the supposed 'peak' level that then gets reported. Indeed it can be hard to know when the true 'peak' level is reached when each new IV dose is infused slowly over a period of sixty minutes. It is, therefore, now generally accepted that, when monitoring *is* called for, 'trough' monitoring is adequate (Miles *et al.*, 1997; Tan *et al.*, 2002).

Since the minimum inhibitory concentration (MIC) for most sensitive organisms is less than 2 mg/l, and since the minimum bactericidal concentration (MBC) is only eight times higher than the MIC, it has long been held that a 'trough' plasma level of 5–10 mg/l is usually very adequate. Although it is now generally thought that a higher trough level (10–15 mg/l) is called for in patients with bacterial endocarditis, little is known as to whether this might increase the risk of toxicity, and co-treatment with rifampicin (q.v.) may be a more appropriate first strategy. The same approach would seem logical when treating infection involving the central nervous system. A similar argument could be advanced about the need to aim for a trough level of 15–20 mg/l when managing what might turn out to become a fulminant methicillin-resistant *Staphylococcus aureus* (MRSA) infection (Gemmell *et al.*, 2006). However, because we do not yet know whether sustained treatment with such a high trough level will be associated with as low an incidence of toxicity as has been the case for the last twenty years (during which time clinicians always aimed for a trough level of 5–10 mg/l.), it seems unwise to recommend the general adoption of a higher trough level than is known to be necessary for the organism currently under treatment.

In essence, while it seems wrong for reference texts in America to continue asserting that a trough level of 5–10 mg/l is always appropriate, it seems equally wrong for the *BNF* and *BNF for children* to imply that a trough level of 15–20 mg/l is always best. Even more perversely, while this text now advises clinicians to aim for a trough level of 15–20 mg/l, the dose regimen recommended is still based on studies that were aiming for a trough level of 5–10 mg/l.

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Managing central nervous system infection

Penetration into the CSF is not very good, and although it increases when the meninges are inflamed (the increase is modest and very variable). It is, therefore, probably sensible to aim for a plasma trough level of 10–15 mg/l, rather than 5–10 mg/l, when managing infection involving the central nervous system, and this may also be one indication for choosing to give a continuous IV infusion (Barois *et al.*, 1986). Chronic low grade staphylococcal infection, of the type associated with contamination of a ventriculo-peritoneal shunt or ventricular reservoir, can be particularly difficult to eliminate, because of the way the organism adheres to the surface of any artificial implant, and treatment in this situation may well call for co-treatment with rifampicin and also, on occasion, intrathecal treatment. Vancomycin has a prolonged half life when given into the ventricles (unless there is substantial CSF drainage), and an intra-thecal or intraventricular dose needs to be chosen that relates not only to the size of the baby, but also to the size of the ventricles and to the rate at which CSF is draining from those ventricles. Clearance rates seem to vary quite widely making it important to measure CSF levels (Bafeltowska *et al.*, 2003). Arnell *et al.* reported in 2007 that, following externalisation of the ventricular catheter, the administration of between 1 and 10 mg of vancomycin once a day into the ventricles in a consecutive series of 34 children nearly always sterilised the CSF within 3 days. Almost all the children in this study had a staphylococcal infection (and, most commonly, a coagulase-negative staphylococcal infection) and two thirds of the children were less than a year old. No adverse effects were encountered using this treatment strategy.

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Potential toxicity

Early reports, when vancomycin first became commercially available, suggested that toxicity could be a real problem. The early recognition that IM administration was painful and that rapid IV infusion could trigger histamine release (the 'red man' syndrome) resulted in a general acceptance that the drug should always be given slowly (conventionally over 60 minutes). Indeed the only reported cases of sudden (happily reversed) cardiac arrest were probably triggered by over-rapid administration. There have also been a few reports of serious neutropenia, usually after prolonged use, but such cases seem to be extremely rare.

The main focus has been on ear problems (ototoxicity) and kidney problems (nephrotoxicity). It seems that the product that first became commercially available probably *did* cause some problems, but there does not seem to be any evidence that the products currently in use have ever caused serious recognisable toxicity. Toxicity has certainly not been reported in infancy with any of the many very variable dosage regimens currently in use. Almost all the early reports of ototoxicity were associated with concurrent aminoglycoside or furosemide use and, in retrospect, these drugs, rather than vancomycin, were almost certainly the products responsible for the damage seen. No evidence of ototoxicity could be detected as a result of treatment with vancomycin in a prospective study of 130 preterm babies who had their automated auditory brainstem responses checked prior to discharge in Rotterdam, even though 20% had trough levels of more than 15 mg/l (de Hoog, *et al.*, 2003). Neither has overt nephrotoxicity been detected (Bhatt-Metha *et al.*, 1999), although very careful assessment has been able to document some transient disturbances of tubular function which seem to resolve completely once treatment is stopped (Ojata *et al.*, 2005; Giapros *et al.*, 2007). If toxicity is sometimes a problem this may well be linked to sustained use rather than to transient high blood levels. Babies are certainly known to have received a ten-fold overdose without experiencing any short term or long term consequences.

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Prophylactic use

IV prophylaxis when giving TPN: The addition of 25 micrograms of vancomycin to each ml of TPN resulted in a very substantial reduction in the number of episodes of coagulase-negative staphylococcal bacteremia in the controlled trials by Spafford *et al.*, and by Kacica *et al.*, in 1994 involving babies weighing less than 1.5 kg at birth, and in the trial by Baier *et al.* 1998 involving babies weighing less than 1 kg at birth. While these trials were not associated with any recognisable increase in the prevalence of vancomycin

resistant organisms, many would hold that prophylaxis is no substitute for an attempt to reduce the risk of such catheter-related infection in the first place, and it is not clear how many cases of overt sepsis, rather than simple transient bacteremia, this strategy prevented. There is still a concern that widespread sustained use could result in an increase in the number of infections caused by vancomycin-resistant organisms. Barefield and Philips said, in an associated editorial, that they had been able to minimise such problems in their unit by only using a central 'long line' in 13% of the babies who weighed less than 1 kg at birth. It is known that long lines seem to become infected five times as often in some units as in others, and this points to the need to stop long lines becoming colonised in the first place, rather than using vancomycin to stop intermittent, transient, low-grade bacteraemia turning into overt septicaemia in those situations where long line use *can* be justified.

Clinicians in Rochester, New York, added vancomycin to all TPN for six years but stopped the practise in 1999 because of fears that such a policy might favour the emergence of vancomycin-resistant organisms. They reported, five years later, that the number of babies treated with vancomycin declined when prophylaxis was stopped, but that the total amount of vancomycin used went up (Elhassan *et al.*, 2004). Blood cultures from babies with a long line in place more often grew Gram-negative organisms in the first time period, while blood cultures from babies with no long line in place were more likely to grow some pathogen in the second time period. The findings would have been more informative if this had been a randomised controlled trial, but the local Research Subjects Review Board misguidedly held that any such trial would have been unethical. As a result we still do not know, more than 12 years after such a strategy was first reported whether such prophylaxis does more good than harm.

In a further, more recent, trial Garland *et al.* (2005) arranged to 'lock' the TPN line for between 20 and 60 minutes two or three times each day with 0.4 ml of 0.9% saline containing 4 units of heparin and 10 micrograms of vancomycin (a volume chosen because it was enough to fill the lumen of both the catheter and the extension tubing with lock fluid). This strategy also resulted in a five fold reduction in the number of what were thought to be catheter-related bloodstream infections, usually due to coagulase-negative staphylococci. While interruption of the TPN infusion in this way not infrequently caused transient hypoglycaemia (≤ 2.2 mmol/l or 40 mg/100 ml), all the babies seemed to remain asymptomatic.

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Prophylactic 'cover' during shunt surgery: A single 'prophylactic' IV dose of vancomycin prior to shunt placement delivers negligible CSF drug levels.

- Le Roux P, Howard MA, Winn HR. Vancomycin pharmacokinetics on hydrocephalic shunt prophylaxis and relationship to ventricular volume. *Surg Neurol* 1990;**34**:366–72.
- Jorgenson L, Reiter PD, Freeman JE, *et al.* Vancomycin disposition and penetration into ventricular fluid of the central nervous system following intravenous therapy in patients with cerebrospinal devices. *Pediatr Neurosurg* 2007;**43**:449–55.

Oral prophylaxis to prevent NEC: 15 mg/kg by mouth once every eight hours for seven days started 24 hours before feeds were introduced halved the risk of necrotising enterocolitis in a randomised trial involving 140 babies weighing less than 1.5 kg at birth in Hong Kong (Siu *et al.*, 1998), and such treatment is known to be associated with very limited systemic drug uptake. Prophylaxis with oral gentamicin (q.v.) seems to be equally effective, but the use of a probiotic (q.v.) is now becoming a more widely used strategy for reducing the risk of this potentially devastating condition in the very preterm baby.

- Siu YK, Ng PC, Fung SCK, *et al.* Double blind, randomised, placebo controlled study of oral vancomycin in prevention of necrotising enterocolitis in preterm, very low birthweight infants. *Arch Dis Child* 1998;**79**:F105–9. [RCT]

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