

AMPHOTERICIN B (Commentary)

Use of amphotericin to treat neonatal Candidiasis

Most *Candida* species are sensitive to amphotericin, and this is particularly true of *Candida albicans*, the most common species. *C. glabrata* and *C. krusie*, which, between them, currently account for about 10% of all infections in children, require a rather higher minimum inhibitory concentration (MIC), but they are still generally considered susceptible. However *C. parapsilosis* is now becoming more common. It has accounted for a quarter of all infections in some series, and 20% of strains were found to be resistant to amphotericin in one recent study from America (Zaoutis *et al.*, 2005), but not in a second from Germany (von Borg *et al.*, 2007).

Amphotericin's fungicidal activity is concentration dependent – it increases as the level of the drug present at the site of infection rises. It also continues to have a therapeutic effect there for many hours after the blood level has fallen, so the key aim has to be to ensure that the peak level exceeds the MIC (Groll *et al.*, 2001). Interestingly however there is no evidence that giving a higher dose than is currently recommended (1–1.5 mg/kg once a day) improves the outcome (Ellis, 2000). Nor does the use of a lipid formulation – the only proven advantage of these, much more expensive, formulations is that they seem to be rather less toxic to the kidney.

Dose regimens for amphotericin

Almost every American text still recommends an incremental approach to dosing using the standard formulation of Amphotericin, but there is *no* evidence that this is necessary in infancy, and such an approach simply means that it may be several days before effective blood levels are achieved and infection is brought under control, especially as the drug has a large volume of distribution. A first test dose is also recommended by many texts, but problems with anaphylaxis have not been described in the neonate. There can be little doubt that a dose of 0.8 to 1 mg/kg is probably necessary if a measurable blood level is to be achieved on the first day of treatment, as Bailey and her colleagues recommended twenty years ago now (Balyey *et al.*, 1990) so it has to be more logical to start with high dose treatment when a child is known to be infected, and then reduce the dose given once effective blood and tissue levels have been achieved.

While there are no formal published papers reviewing the use of the strategy suggested here, over 20 years experience in Sydney and in several of the larger 'teaching' hospitals in London seem to support the safety and appropriateness of such an approach. It is the policy that has been recommended by this *Formulary* since 2000, the policy recommended in 6th and 7th editions of the Queen Charlotte's and Hammersmith Hospitals' *Neonatal Formulary*, and the strategy that was recommended in the *Handbook of Neonatal Infections* by Isaacs and Moxon in 1999. It also finally became the policy recommended by the *British National Formulary for Children* in 2008.

Side effects with such a policy are much less common than most reference texts would lead readers to believe, and can be managed by reducing the dose used or changing to the liposomal product. However there is no evidence that any one lipid preparation is better than any other, and no evidence that the liposomal product (Ambisone[®]) is any more effective in curing a child of fungal infection than the standard formulation. Given that it costs twenty times as much there is, therefore, little justification for routinely using the more expensive product. It is also important to be aware that deteriorating kidney function may be caused by fungal infection of the renal tract and should not necessarily be interpreted as evidence of drug toxicity. Indeed it needs to be appreciated that the very process that makes the drug less toxic also reduces its ability to clear infection from the renal tract (Wong-Beringer *et al.*, 1998).

Combined treatment with flucytosine (q.v.) serves to treat possible CSF infection (Almirante and Rodriguez, 2007), serves to bring treatment under control more quickly and, because it acts synergistically, makes it possible to give a lower dose of amphotericin. Treatment with caspofungin should be considered if fungal infection does not seem to be responding to management along standard lines. A full monograph for this relatively new and very expensive drug was posted on the *Formulary* web site in July 2008.

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Treatment of leishmaniasis

Visceral leishmaniasis (kala-azar) remains a significant problem in many tropical and subtropical parts of the world. The identification of parasites in smears taken from splenic or marrow puncture is diagnostic, but the former is potentially hazardous, while the absence of parasites in the marrow does not mean that the patient is uninfected. However a range of new serological tests are now becoming more widely available, including an immunochromatographic strip test using the rK39 antigen, while a latex agglutination test (KATEX), based on the detection of antigen in urine, has also been described. A polymerase chain reaction (PCR) test for detecting parasitic DNA has also been developed. Treatment has, until recently, been from satisfactory and most drugs are potentially toxic. While pentavalent antimony compounds have been used for over 70 years, and are cheap, parasitic resistance is now becoming an increasing problem in some areas. All the lipid-associated amphotericin B products can, however, be rapidly curative. Even a single 5 mg/kg dose of AmBisome cures more than 90% of all patients (Sundar *et al.*, 2001), but many have given 20 mg/kg a day for two days (Minodier *et al.*, 2005). Indeed a range of oral treatment strategies are currently under development (Sundar and Kumar, 2005). Such evidence as there is suggests that such treatment is also safe when visceral leishmaniasis calls for treatment during pregnancy (and untreated infection can have serious consequences for both the fetus and the mother).

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