

FLUCONAZOLE (Commentary)

Prophylactic use in very preterm babies

Use of fluconazole: Systemic *Candida* infection is currently encountered in some 7% of all babies weighing less than 1 kg at birth in the America (Benjamin *et al.*, 2006), but in only about 2% of these babies in the UK (Clerihew *et al.*, 2006). Prevalence varies widely – the problem is commoner in some units than in others, and in some countries than in others. Almost a third of all the children of less than 1.5 kg at birth in the placebo arm of a recent Italian trial were colonized, and 13% developed invasive fungal infection (Manzoni *et al.*, 2007). The prognosis for the 7% of babies of less than 1 kg at birth who *did* develop systemic *Candida* infection while receiving care in a NICHD Research Network Hospital in America in 1998–2001 was very poor: a third died and half the survivors showed evidence of neurodevelopmental impairment at 18–22 months (Benjamin *et al.*, 2006). Systemic infection often persisted for many days, especially if the ‘long line’ was not removed or replaced within a day, and a single negative blood culture could not be relied upon to show that infection had been eradicated (as Chapman and Faix, and Karlowicz *et al.*, had found eight years earlier). Indeed half the babies with fungal CNS infection in the NICHD study had had at least one falsely reassuring negative blood culture. The use of a cephalosporin, and delayed enteral feeding, both made systemic infection more likely. In another recent study (Feja *et al.*, 2005) systemic fungal infection was also more common in babies who had previously had a documented episode of bacterial sepsis or evidence of necrotizing enterocolitis – a feature that strongly suggests that widespread broad-spectrum antibiotic use is a major contributory factor.

There has, as a result, been mounting interest in the **prophylactic** use of oral or IV fluconazole to keep colonisation in check, and so reduce the risk that this will then evolve into systemic fungal infection. Such an approach was described some years ago in the management of patients with AIDS and with leukaemia, and validated in at least two randomized controlled trials (Leen *et al.*, 1990; Winston *et al.*, 1993). However, in a more recently published trial, its more general empirical use was not found to improve outcome in seriously ill adults in intensive care with an unexplained fever despite antibiotic treatment (Schuster *et al.*, 2008). Similarly, while a meta-analysis of four trials of its routine use in adult patients required surgical intensive care (Shorr *et al.*, 2005) found that fluconazole halved the rate of documented fungal infection, it did little to improve survival rates.

A steady stream of observational studies have been published since 2001 suggesting that prophylaxis can also be useful the very low birth weight baby, and a meta-analysis of four randomised trials have now confirmed that such an approach does reduce the risk of invasive fungal infection (Clerihew *et al.*, 2008). There is also a suggestion from the largest of these four trials – an Italian study involving 322 babies of less than 1.5 kg – that *low* dose prophylaxis (3 mg/kg IV or by mouth once every three days for two weeks and then once every other day for another 2–4 weeks) started routinely three days after birth may be just as effective as a dose twice this big (Manzoni *et al.*, 2007).

Many are now recommending routine prophylaxis for all high risk babies “early enough to prevent colonization, ideally on the first postnatal day” and continuing this for 36 weeks (Healy and Baker, 2009). However, such views still leave many skeptical as to whether *routine* prophylaxis is really wise (Neely and Schreiber, 2001; Long and Stephenson, 2005; Benjamin, 2008) and there is, as yet, no evidence that the decrease in the incidence of overt fungal infection leads to any improvement in survival to discharge, or in the risk of disability in those who do survive. Similarly, while there is little evidence that the widespread use of fluconazole has yet started to cause drug resistant fungal strains to emerge (Roilides *et al.*, 2004; Healy *et al.*, 2008; Manzoni *et al.*, 2008), there are signs that this could happen (Sarvikivi *et al.*, 2005; Giusiano *et al.*, 2005; Khan *et al.*, 2007), and it could become a serious problem with widespread use. Several groups are certainly now suggesting that a more selective approach that targets just the most vulnerable babies for short-term treatment may be a wiser strategy (Uko *et al.*, 2006; McCrossan *et al.*, 2008).

Alternative strategies: Some would even suggest that the prophylactic use of a systemically absorbed drug to deal with a problem that is probably caused by excessive broad spectrum antibiotic use in the first place is the ‘lazy option’, and that more should be done to try and find out *why* systemic fungal infection is so much more common in some units than it is in others. If heavy colonization of the skin and intestinal tract with *Candida* was not so prevalent in the first place, near universal prophylaxis would not be necessary. One reason may be that some units use IV alimentation for much longer than others, and another that units also vary in the diligence with which these lines are inserted and cared for (O’Grady *et al.*, 2002; McGee and Gould, 2003)

There is also at least one simpler and cheaper approach that has, to date, gone largely ignored. A small single-centre trial involving 67 babies weighing less than 1.25 kg at birth (Sims *et al.*, 1988) showed, twenty years ago, that the prophylactic use of oral nystatin (which is not absorbed into the blood stream when given by mouth) could also substantially reduce the risk of systemic fungal infection (32 v. 6%). Recent

studies from France (Borderon *et al.*, 2003), from Turkey (Ozturk *et al.*, 2006), and from America (Srinivasan *et al.*, 2007), have confirmed that, if hand washing is done carefully enough to prevent *Candida* spreading from patient to patient, and if oral nystatin is started as soon as colonisation is suspected, systemic fungal infection becomes rare even in very low birth weight babies. An observational study in Liverpool between 1998 and 2003 also seemed to show that prophylaxis with nystatin is capable of reducing the incidence of invasive fungaemia (Ganesan *et al.*, 2009), and an even larger observational study from Australia covering the years 1993 to 2006 came to the same conclusion (Howell *et al.*, 2009). Professor Manzoni and his colleagues have wondered whether the use of nystatin may be masking the true incidence of invasive *Candida* infection, and would argue that any definition of systemic infection must, at the very least, include all cases where *Candida* is cultured from urine, CSF or peritoneal fluid as well as from blood (Manzoni *et al.*, 2009). Most would however agree with the conclusion of this recent review that routine fluconazole prophylaxis is probably not indicated in any unit where, with other approaches to general care, fewer than 5% of the babies at greatest risk are currently developing systemic infection.

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Efficacy and pharmacokinetics

Postnatal age has a significant impact on the pharmacokinetics of fluconazole, but this is a subject that has been reasonably well studied. While oral treatment delivers blood levels that are almost as high as IV treatment, there is increasing evidence that most reference texts currently recommend a dosage regime for the neonate that may well not be therapeutic if the *Candida* organism involved has a moderately high minimum inhibitory concentration (MIC), and Wade *et al.* 2009 have recommended a dose of 12 mg/kg once a day in order to be sure of giving enough to eliminate systemic infection where the organism has a MIC of $\leq 8 \mu\text{g/ml}$. They also point that, given the long half life, such a level will not be achieved for 2–3 days if no initial loading dose is given. Although this is the dose now recommended by this *Formulary*, its safety requires further study. There is one report suggesting that neonatal use may be associated with a higher incidence of cholestasis (Aghai *et al.*, 2006), but no such association could be found after allowing for the confounding effect of the common use of parenteral nutrition in a later larger study (Healy *et al.*, 2008). Widespread neonatal use both to prevent and to treat *Candida* infection does not seem to have resulted, as yet, in the emergence of many organisms that are resistant to this useful antifungal drug, but it is a problem that could arise at any time (see above). Maternal treatment during lactation only exposes the baby to ~10% of the weight-adjusted maternal dose, and no authority has ever suggested that such exposure could be harmful.

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Slow IV administration

Many texts offer very firm advice as to how quickly it is safe to give this drug IV, but few state the reasoning behind the advice on offer, and the advice varies to widely that much of it must be wrong. Most paediatric texts in the UK including the *BNF* and *BNF-C* suggest that fluconazole can be given over 10–30 minutes, but one major American reference text (Taketomo's *Pediatric Dosage Handbook*) says it should be given "over 1–2 hours". The manufacturer's advice in the UK is that adults can normally be given their standard 200 mg IV dose over about 10 minutes, but the advice offered in America is that this dose should be given over an hour. Australian texts offer similar advice. There are no reports to suggest that rapid bolus administration is toxic, and no adverse reports associated with slow (but untimed) IV administration given over about 10 minutes in the manner advocated on page 6 of this *Formulary*.

Taketomo CK, Hoddling JH, Kraus DM, eds. *Pediatric dosage handbook. Including neonatal dosing, drug administration & extemporaneous preparations*. 16th ed. Hudson, Ohio: Lexi-comp; 2009.

British National Formulary. *BNF for children*. London: Royal Pharmaceutical Society, 2009.

Use during pregnancy and lactation

High dose systemic exposure (400 mg/day) in the first trimester of pregnancy can produce a constellation of serious fetal abnormalities, but there are, as yet, no reports of teratogenicity with a single 150 mg dose in the first trimester, or with topical or oral use later in pregnancy. Systemic use by the mother during lactation will result in the baby receiving a substantial amount of the drug (~10% of the maternal dose on a weight-for-weight basis), but there is, as earlier sections of this review have shown that, no evidence that exposure to the much higher doses used during routine prophylaxis ever does any harm, so mothers should not be allowed to worry about the fact that a small amount of any fluconazole that they take systemically will ever harm the baby.

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Candida as a cause of maternal nipple pain

Superficial, and more particularly deeper, ductal, *Candida* infection is now widely thought to be responsible

for the severe radiating nipple pain that some women experience during breast feeding. It is, however, a very poorly studied subject. Health professionals have subjected the issue to very little study while lay groups, who have very extensive experience of this issue, have found it almost impossible to get the funding needed to study the subject rigorously. Similarly, the drug company that initially had the patent for this product can see no point in funding the study of this problem (or making a move to get the product licensed for such use) because that patent has now expired..

Most pain, especially pain experienced when feeding is first becoming established, is due to poor positioning – an easily solved problem as long as the mother can get access to experienced support and advice from a group such as the UK Breastfeeding Network (whose help line is 0844 412 4664), the Australian Breastfeeding Association, or the La Leche League International in America. [See: www.breastfeedingnetwork.org.uk; www.breastfeeding.asn.au; and www.lalecheleague.org.] Unresolved engorgement, eczema, tongue-tie, are other occasional causes of pain. A suddenly tender, lumpy and inflamed breast is evidence that mastitis is developing, a problem reported at least once during a tenth of all lactations (Foxman *et al.*, 2002). Frequently, however, this is simply due to a breast duct becoming blocked, although secondary staphylococcal infection can occasionally develop as a result of this (Inch and Fisher, 1996), meriting antibiotic treatment (as outlined in the *Formulary* monograph on flucloxacillin).

Features that are held to suggest that the pain could be due to *Candida* infection include bilateral burning or stabbing pain, and pain that increases in intensity after a breastfeed has finished, and continues for up to an hour afterwards (Francis-Morrill *et al.*, 2004). A few cases seem to be a form of Raynaud's phenomenon (Anderson *et al.*, 2004), and this occasionally merits pharmacological intervention – giving these mothers a 30 mg slow release tablet of nifedipine (Adalat[®] Retard) once a day often brings rapid relief. The absence of pyrexia, or of a localized red area on the breast, are suggestive, and many would hold the diagnosis to be much more plausible if the mother has recently had antibiotic treatment, and there are signs to suggest that the baby has oral thrush. Many feel that the appearance of the breast is of little help, although it is sometimes said that the nipple may become unusually pale, or tender and fiery red. It has only proved possible to culture *Candida* from a proportion of surface swabs and milk samples, and the results do not seem not to be reliable or informative enough to make this worth doing.

That very shrewd and experienced clinician Mavis Gunther noted that painful fissured nipples could often be colonized by *Candida* more than sixty years ago, but the entity only seems to have been widely written about for the first time by the Australian family planning doctor Lisa Amir in 1991, and the only two formal studies of the condition still remain the study that she summarized in 1996, and the study reported by the medical student Karen Tanguay from a breast feeding clinic in Calgary, Canada in 1994. Nevertheless, by the end of the decade the condition was accepted as a proven entity by almost every Board Certified Lactation Consultant and every member of the Academy of Breastfeeding Medicine in America (Brent, 2001). Others have remained more skeptical (Carmichael and Dixon, 2002) and Thomas Hale, the Pharmacist who has written the world's most widely read book on "Medications and Mothers' Milk", (www.ibreastfeeding.com) has recently begun to express doubt as to whether the condition really exists.

Such skepticism baffles those who have experienced rapid symptomatic relief within 3–4 days once finally started on antifungal treatment, but there is little doubt that the condition is currently over-diagnosed. It can not be stressed too strongly that poor positioning is by far the commonest cause of nipple pain and nipple trauma and not drug treatment is going to compensate for that. Nevertheless, once an experienced breastfeeding advisor has ruled out most other possibilities, a trial of treatment is the only effective way to make a positive diagnosis (and important to remember that poor positioning, nipple trauma, and active *Candida* infection can probably all co-exist).

Management: Treatment is only going to be effective if the mother and baby are both treated, and re-infection may well occur unless all dummies, nipple shields, bottle teats and plastic toys are washed and sterilised (and this may involve boiling everything for twenty minutes). Take great care with the disposal of nappies, and wash your hands meticulously afterwards. Try and ensure that each member of the family has a separate towel. Treat possible oral thrush with miconazole oral gel (q.v.), smearing 1 ml of the gel carefully round the child's mouth and gums after a feed four times a day (Hoppe, 1997) and, simultaneously, smear a *small* amount of 2% miconazole cream on the nipples after every feed (while remembering to wipe anything that is still visible away again before starting the next feed). Do not be put off by the fact that the manufacturer has recently said they do not think the oral gel is safe to use in children less than 4 months old – this change of advice seems to have been triggered by a single report of a Dutch baby who choked badly after the mother smeared large amounts of the gel on her nipples immediately before putting her baby to the breast (De Vries, *et al.*, 2006). The change of advice was widely criticized as a quite unjustified defensive over-reaction to an event that caused no lasting harm and was simply due to the inappropriate use of the appropriate drug.

If the baby has more extensive *Candida* infection, there may be a case for giving nystatin as oral drops and/or ointment (q.v.). And do not be reluctant to offer the mother pain relief merely because she is breast

feeding. Most mothers can be offered two 400 mg tablets of ibuprofen three times a day after food, while those who are asthmatic, have a stomach ulcer or are allergic to aspirin can, as an alternative, be advised to take two 500 mg tablets of paracetamol three or even four times a day.

Those with extensive experience of this condition believe that, if infection of the breast has become deep seated, it will only be eradicated if the mother is also given a course of oral fluconazole (even though the manufacturers do not have a license to recommend such treatment). Give an initial 150–300 mg loading dose, and then 50–100 mg twice a day by mouth for at least ten days. The symptoms should start to improve within three days and the diagnosis needs to be reconsidered if there is no improvement after a week, but treatment sometimes needs to be sustained for more than ten days if symptoms have been present for a long time.

Many have expressed concern at the thought of prescribing a systemic antifungal drug that is known to appear in human milk and be absorbed by the baby for some supposed infection for which there is no objective evidence. There are, however, many other conditions where we accept that a diagnosis has in fact been made if some quite specific treatment causes rapid symptomatic relief, and those who criticise the use of fluconazole, except in the context of a formal research trial, for a problem that shows every chance of bringing breast feeding to an end if no solution is quickly found, ought to be even more critical of the widespread prophylactic use to which the drug is now being put (see above) simply to reduce the risk of infection!

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