Antifungal prophylaxis in neonatal intensive care units

Survival of extremely preterm babies is increasing and invasive fungal infection is an emerging problem in this vulnerable population. Fungal sepsis is associated with a higher mortality and worse neurodevelopmental outcome than bacterial sepsis alone. The reported incidence varies widely amongst units. Prophylactic antifungal drugs reduce fungal colonisation and infection rates in very low birthweight babies. In this review we discuss the potential benefits and risks of fungal prophylaxis.

Joanne Hegarty
MB BCh BAO MRCPCH
Regional Neonatal Intensive Care Unit, Royal Jubilee Maternity Hospital, Belfast, Northern Ireland.

David G Sweet
MD FRCPCH
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Royal Jubilee Maternity Hospital, Grosvenor Road, Belfast, Northern Ireland.
david.sweet@belfasttrust.hscni.net

Keywords

antifungal prophylaxis; invasive fungal infection; extremely low birthweight; very low birthweight; fluconazole; nystatin

Key points

Hegarty J., Sweet D.G. Antifungal prophylaxis in neonatal intensive care units. *Infant* 2009; 5(3): 90-93.

1. Ten per cent of all nosocomial/late onset sepsis in VLBW babies is fungal.
2. Mortality and neurodevelopmental outcome is worse than for babies with bacterial sepsis.
3. Prophylactic antifungal drugs have been shown to reduce fungal colonisation and infection rates in VLBW babies.
4. Incidence rates vary across countries and NICUs.
5. Selecting babies at highest risk of invasive fungal sepsis for antifungal prophylaxis may reduce the number needed to treat to achieve benefit.

Survival of extremely preterm babies is increasing and fungal infection is an emerging problem in this vulnerable population. Invasive fungal infection is defined as positive fungal cultures from blood, cerebrospinal fluid or urine (collected by suprapubic aspiration or bladder catheterisation). Early diagnosis of fungal infection can be difficult as it often has a similar presentation to bacterial infection. Babies may present insidiously with poor colour, elevated C reactive protein and falling platelets in the absence of positive bacterial cultures. It is therefore important to maintain a high index of suspicion and to consider screening specifically for fungal infection in at-risk babies when signs of sepsis are present and they are not responding to antibiotics in the usual way.

Invasive fungal infection is usually nosocomially acquired. It accounts for approximately 10% of all first episodes of late onset sepsis in very low birthweight (VLBW) babies[1]. The incidence peaks between 2-6 weeks of age and in the UK the median age at diagnosis is 14 days[2]. *Candida albicans* is the most commonly cultured fungal organism and the third most frequent cause of late-onset sepsis in the VLBW baby[1]. *Candida parapsilosis* makes up about 25% of cases of fungal infection[2]. The diagnostic sensitivity of blood culture for invasive fungal infection is low at approximately 50%, and therefore the true incidence may be under-represented[2].

Preterm, VLBW babies are at greatest

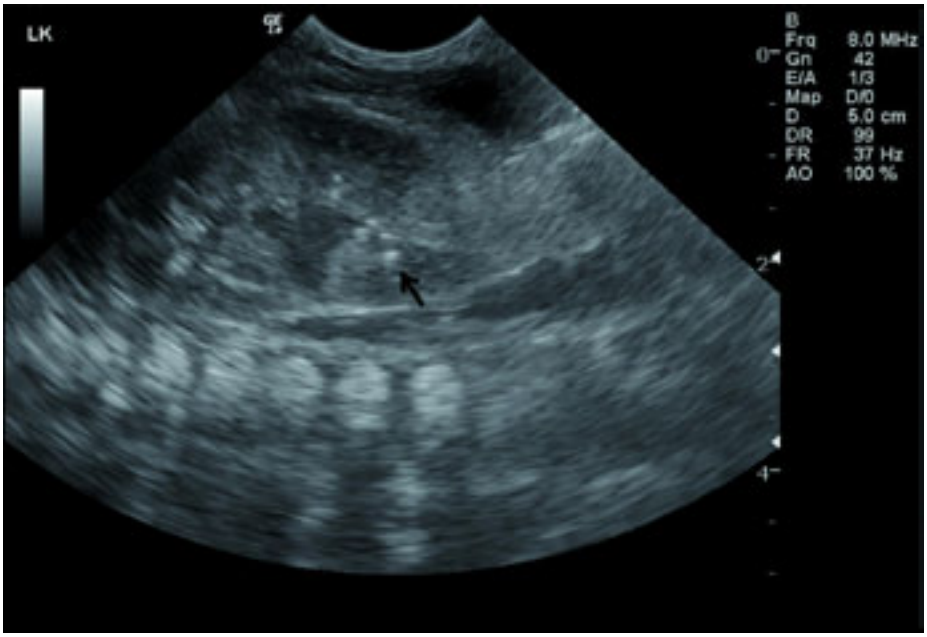

FIGURE 1 Renal ultrasound of fungal balls – the arrow points to an area of increased echodensity in keeping with a renal fungal ball.

Name	Route	Dose	Evidence for use
Miconazole	Oral	1mL 2-4 times daily smeared around the mouth after feeds[27]	One RCT: no significant effect on invasive fungal infection
Nystatin	Topical or oral	100,000 U in 1mL 8 hourly[10]	Two RCTs: significant reduction in invasive fungal infection
Fluconazole	Oral or intravenous	<2 weeks of age: 6-12 mg/kg every 72 hours[27] >2 weeks of age: 6-12 mg/kg every 48 hours[27]	Meta-analysis: significant reduction in invasive fungal infection
Amphotericin B with flucytosine	Intravenous	Amphotericin B: dependent upon brand used[27] Flucytosine: 50mg/kg iv 12 hourly[27]	No trials in neonatal population

TABLE 1 Drugs reported to have been used in antifungal prophylaxis.

risk of invasive fungal infection. If fungal infection is suspected in this population, fungal cultures should be sent and in addition to this other investigations such as renal ultrasound, echocardiography, and ophthalmic assessment should be considered as they may reveal evidence of disseminated candidaemia (**FIGURE 1**).

Treatment is with intravenous antifungal drugs such as fluconazole or amphotericin B and flucytosine, usually for a period of 4-6 weeks. During this time all central venous catheters usually need to be removed. The drugs can have significant side effects necessitating monitoring of renal and hepatic function and clearly prevention of fungal infection would be considered better than cure. Prevention should also be considered a priority because of the associated poor outcome following invasive fungal infection, with one study of extremely low birthweight (ELBW) babies from the USA showing a combined outcome of neurodevelopmental impairment or death of 73% in those with either bloodstream or cerebrospinal candidal infection[3]. These outcomes are much worse than for babies with bacterial sepsis alone. VLBW babies with invasive fungal infection are twice as likely to die as those with bacterial late onset sepsis (OR dying with fungus versus other organisms 2.0 [95% CI 1.3-3.0])[1].

Prophylactic antifungal drugs have been shown to reduce fungal colonisation and infection rates in randomised trials in VLBW babies[4]. However these studies collectively do not show convincing reductions in mortality and appear to take place in units with very high rates of invasive fungal infection in the placebo arm of the trials. There are concerns about widespread use of antifungals because of the potential for toxic side effects and drug resistance. Clinicians remain in equipoise regarding universal fungal prophylaxis[5-7]. Some centres have adopted routine prophylaxis. Others have attempted to limit exposure to prophylactic antifungals by selecting babies with additional risk factors for fungal sepsis, such as exposure to cephalosporins, and they too report reductions in fungal infection rates. In this review we discuss the potential benefits and risks of fungal prophylaxis in VLBW babies.

How much of a problem is invasive fungal infection in neonatal units?

Fungal colonisation of the skin and gastrointestinal tract usually precedes invasive fungal infection. Colonisation is acquired vertically from maternal vaginal candidiasis or horizontally from carer hand colonisation. Some units routinely screen for candidal skin and rectal colonisation. At birth 5-10% of babies can be shown to be colonised and this increases to 60% of those in NICU by one month of age[8,9]. By reducing colonisation we may be able to reduce invasive fungal infection and this theory has led to the studies of antifungal prophylaxis[9].

Invasive fungal infection appears to predominantly affect the smallest and most immature babies, being three times more common in babies with a birth weight less than 750g than in those of 750g to 1000g[4]. The actual rates of invasive fungal infection are very difficult to determine. Those reported in the placebo arms of the randomised trials vary widely between units and in some studies are as high as 32%[10]. In a UK survey in 2004 invasive fungal infection occurred in 2.1% of babies of <1000g and 1% of those <1500g birth weight[2]. These differences in incidence can be attributed to demographics of admission policies, resuscitation practice, surgical population, feeding and antibiotic practice and other risk factor practice such as endotracheal intubation and central venous catheters.

Antifungal prophylaxis

Nosocomial infections including *Candida* can be reduced by standard infection control measures such as handwashing, aseptic intravascular catheter handling, minimising duration of total parenteral nutrition and endotracheal intubation and rationalisation of intravenous antibiotic use. Antifungal prophylaxis should be considered in addition to these routine practices. There is no consensus regarding which drugs should be used and the list of all drugs which are reported to have been used is shown in **TABLE 1**. As only nystatin and fluconazole have been proven to reduce invasive fungal infection in the NICU setting we will limit our discussion to the use of these two drugs.

A UK survey in 2007 showed that of the 93% of neonatal intensive care units which responded, 28% were using topical/oral/systemic antifungal prophylaxis[5]. Two surveys of neonatologists within the last five years have shown that 34% of respondents in the USA and 53% in the UK and Ireland were using antifungal prophylaxis. The commonest reasons given for not using prophylaxis were concerns about resistance and the need for further research. Neonatologists in the UK and Ireland also perceived that the incidence of invasive fungal infection was not of a high enough level in their unit to justify routine prophylaxis[6,7]. Some units have developed policies to select babies perceived to be at very high risk of invasive fungal infection and limited prophylaxis to this group (see later).

Nystatin

Nystatin is a polyene, a non-absorbable antifungal, which when given orally reduces gastrointestinal and skin colonisation[10]. A small randomised controlled trial in 1988 of nystatin antifungal prophylaxis in babies of 500-1250g showed a reduction in colonisation and invasive fungal infection. Of the 67

babies recruited, 33 were treated with nystatin. The invasive fungal infection rate was 32% in the control and 6% in the treatment group (P<0.001)[10]. A more recent and larger Turkish study recruited almost 4000 babies of all weights and gestations. Overall this showed that prophylactic nystatin significantly reduced invasive fungal infection, with rates of 14.2% in the control arm, 5.6% in the group treated only when colonised and 1.8% in the group treated prophylactically[11]. However it is difficult to generalise the data from this trial. Most of the benefit was found in the group who were <1500g birthweight, but the rate of invasive fungal infection of 44% in the corresponding placebo arm was incredibly high. Units with lower rates of invasive fungal infection are less likely to see the same benefits. The current Cochrane review states that there is not enough evidence to support the use of oral nystatin for prophylaxis in the VLBW baby. However it may offer significant protection and many units are now routinely administering oral nystatin to babies perceived to be at risk[5, 6, 7, 12]. A recent review by Isaacs suggested that oral nystatin prophylaxis should be used routinely for VLBW babies and that fluconazole be used when the rate of fungal infection remains high despite attempts to minimise risk factors[13].

Fluconazole

Fluconazole is a member of the triazole antifungals. It targets all sites of potential colonisation and dissemination and due to its excellent bioavailability can be used orally as well as intravenously with good tissue penetration. Interest grew in fluconazole prophylaxis following a single-centre randomised controlled trial in ELBW babies which showed a reduction in invasive fungal infection in the fluconazole prophylaxis group[14]. Fluconazole antifungal prophylaxis in VLBW babies has been reviewed in a Cochrane meta-analysis of four randomised trials which shows a significant decrease in invasive fungal infection. [RR 0.23; 95%CI (0.11-0.46). NNT 9; 95% CI (6-17)]. There was also a trend to decreased mortality [RR 0.61; 95%CI (0.37-1.03)][4]. To date there have been no significant adverse effects described and no resistance reported in newborn babies but it is important to remain vigilant.

One paper reported that a strain of *Candida parapsilosis* less sensitive but not resistant to fluconazole was identified in a neonatal intensive care unit where fluconazole antifungal prophylaxis had been in use for 10 years[15]. A Cochrane review of immunocompromised adults on fluconazole prophylaxis showed an increased risk of colonisation but not of invasive candidal infection[16]. A recent single-centred, retrospective study showed no increase in natively fluconazole-resistant *Candida* subspecies in the six years following introduction of routine fluconazole prophylaxis to all VLBW babies[17].

Concerns have also been raised as to whether invasive fungal infection is less likely to be diagnosed in those receiving antifungal prophylaxis because of reduced sensitivity of microbial culture in the presence of fluconazole[4]. Strategies including lower dose and less frequent administration may reduce the risk of resistance developing. An Italian multi-centred, randomised placebo-controlled trial of two different doses for prophylaxis showed that 3mg/kg and 6mg/kg fluconazole were equally effective when used as prophylaxis in VLBW babies. Of the 322 babies recruited, the incidence of invasive fungal infection was 2.7% in the 6mg group, 3.8% in the 3mg group and 13.2% in the placebo group[8]. A single-centred randomised placebo-controlled trial showed that twice weekly dosing with 3mg/kg was as effective as a more frequent dosing regimen in ELBW babies[18].

Fluconazole appears to be a very safe drug. No significant differences have been shown in rates of bacterial infection, necrotising enterocolitis or abnormal liver function tests in newborn babies receiving fluconazole antifungal prophylaxis. Two studies have shown a transient effect on cholestasis which resolves when the drug is stopped[19, 20]. There is still only limited long term data on the effect of fluconazole antifungal prophylaxis on neurodevelopmental impairment, although no particular reason for concern.

- Fungal colonisation
- Use of third generation cephalosporins
- Prolonged broad spectrum antibiotic use
- Multiple antibiotics
- Total parenteral nutrition with lipids
- Endotracheal intubation
- Central venous catheterisation
- Previous blood stream infection
- Postnatal steroids
- Severe illness at birth
- H_2 receptor antagonists
- Gastrointestinal disease or surgery

TABLE 2 Additional risk factors for invasive fungal infection.

Selecting a population for prophylaxis

One approach to limiting exposure to antifungal agents is to select babies at highest risk of invasive fungal infection for antifungal prophylaxis. This may be especially appropriate in the UK where the reported incidence is much lower than in the published randomised trials, making the number needed to treat to achieve benefit much higher. The additional risk factors for invasive fungal infection are shown in **TABLE 2**.

Several single-centred observational studies have reported a reduction in invasive fungal infection in a targeted population of high risk babies given fluconazole prophylaxis of a similar magnitude to the differences shown in randomised trials. The criteria used to select the 'high risk' groups varied between studies and combinations of risk factors chosen were as follows:

- ELBW with intravenous access or endotracheal tube *in situ* within the first six weeks of life[14].
- Less than 32 weeks' gestation and VLBW on broad spectrum antibiotics[19].
- VLBW with central venous access[21].
- VLBW with central venous access and candidal colonisation or third generation cephalosporin treatment or total duration of intravenous antibiotics of more than 10 days[22].
- Less than 26 weeks' gestation and/or 750g birth weight with central venous access[23].

Each of these studies reported significant reductions in invasive fungal infection rates whilst avoiding prophylaxis based on weight criteria alone. If adopting this approach, it is vital that each unit consider their own data for invasive fungal infection to determine risk factors in their own population[23].

Kaufman suggests using an infection surveillance chart to assist in defining target population within a unit[24]. For example this might lead a particular unit to select only those babies of less than 26 weeks' gestation for antifungal prophylaxis after discovering that their unit only sees invasive fungal infection in this group of patients.

The future

Invasive fungal infection remains an important, if uncommon problem in NICUs in the UK. In units with an incidence of invasive fungal infection similar to that of the UK national figure it is estimated that 130 VLBW or 62 ELBW babies would need to be given fluconazole prophylaxis in order to prevent one case of invasive fungal infection[25]. This is in contrast to the rates seen in units in other countries which participated in the randomised trials where potentially only eight VLBW or five ELBW babies would need to be treated to achieve benefit[8]. This needs to be borne in mind when considering prophylaxis policies, and consideration should be given to limiting antifungal exposure to only those babies perceived to be at the highest risk.

Further research is needed to compare fluconazole and nystatin with placebo and studies need to be large enough to ascertain the effects on important outcomes such as mortality and disability free survival. Potential emergence of drug resistance remains a concern and needs continued surveillance. The timing of initiation of prophylaxis should be further investigated as treatment before colonisation appears more effective[8,26]. With such high risks of poor outcome in invasive fungal infection, NICUs should continue surveillance and if necessary consider targeting the prevention of invasive fungal infection as an area of quality improvement.

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