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[Intervention Review]

Antifungal therapy for newborn infants with invasive fungal infection

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ABSTRACT

Background

A variety of antifungal drugs, drug preparations and drug combinations are available to treat newborn infants with suspected or confirmed invasive fungal infection. There is a need to assess their relative merits.

Objectives

To assess the effect of treatment with different antifungal drugs, drug preparations or drug combinations on mortality and morbidity in newborn infants with suspected or confirmed invasive fungal infection.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2012, Issue 2), MEDLINE, EMBASE, CINAHL (to March 2012), conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised control trials comparing one antifungal agent or combination of agents with another in newborn infants with suspected or confirmed invasive fungal infection.

Data collection and analysis

We extracted the data using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by each author, and synthesis of data using risk ratio and risk difference.

Main results

We identified only one small trial in which 24 newborn infants participated. This trial compared the use of fluconazole versus amphotericin B (plus 5-fluorocytosine if fungal meningitis present). The trial did not detect a statistically significant effect on mortality (risk ratio 0.73; 95% confidence interval 0.26 to 2.05).

Authors' conclusions

There are insufficient data to inform practice. Large randomised controlled trials are required to compare antifungal drugs, drug preparations or drug combinations for treating newborn infants with invasive fungal infection.

PLAIN LANGUAGE SUMMARY

Systemic antifungal drugs for invasive fungal infection in preterm infants

Preterm and sick newborn infants are at risk of serious infections of the blood, brain and kidneys due to fungi such as *Candida* (the organism that causes thrush). Severe fungal infections are associated with high death rates and with long-term brain damage in newborn infants. A variety of different types of drugs for treating fungal infections are available. However, this systematic review found only very limited evidence (one small trial) to support the use of one type of antifungal drug over another. Until this uncertainty is resolved with new large trials, clinicians may continue to base their choice of antifungal agent on data extrapolated from studies in older children and adults.

BACKGROUND

Description of the condition

Invasive fungal infection, predominantly due to *Candida* species, is an increasingly common cause of mortality and morbidity in preterm and sick newborn infants (Robinson 2009). The increase in incidence over the past 25 years may be due to the increased survival rates for preterm and sick infants and the invasive and intensive nature of the care that these infants receive. Invasive fungal infection accounts for about 10% of all cases of late-onset invasive infection (diagnosed > 72 hours after birth) in newborn infants. Preterm birth and low birth weight are the most important independent risk factors. The estimated incidence is 2% to 5% in very preterm or very low birth weight (VLBW) infants (Clerihew 2006; Vergnano 2011). In extremely preterm or extremely low birth weight infants, the incidence has been estimated to be as high as 10% (Karlowicz 2002). Other specific risk factors for invasive fungal infection include fungal colonisation, severe illness at birth, the use of multiple courses of antibiotics, the use of parenteral nutrition, the presence of a central venous catheter and the use of histamine receptor subtype 2 antagonists (Saiman 2000; Benjamin 2006; Blyth 2009).

In addition to fungaemia, infants may develop fungal pneumonia, meningitis, renal tract infection, ophthalmitis, osteomyelitis, endocarditis, liver abscesses and skin abscesses (Benjamin 2003; Clerihew 2006). The estimated attributable mortality of invasive fungal infection in newborn infants is about 25%, higher than that associated with invasive bacterial infection (Stoll 1996; Saiman 2000; Makhoul 2002; Stoll 2002; Benjamin 2003; Blyth 2009). Invasive fungal infection is also associated with short- and long-term morbidity. In particular, fungal infection of the central nervous system has a significant impact on long-term neurodevelopmental outcome (Friedman 2000; Benjamin 2003).

Description of the intervention

Three classes of antifungal drugs are commonly available for treating newborn infants with invasive fungal infection (Frattarelli 2004).

Polyenes

The most commonly used drug is amphotericin B, a polyene antifungal agent that reacts with sterols in cell membranes to cause cell lysis. Amphotericin B is poorly absorbed via the enteral route and is given as an intravenous preparation. Drug toxicity, particularly nephrotoxicity, is a potential problem as amphotericin B also damages mammalian cell membranes. These adverse effects limit the total dose that may be given. The newer lipid complex formulations of amphotericin B deliver the active drug directly to the site of action on the fungal cell membrane. Because the lipid complex is more stable in mammalian cells, toxicity is reduced. Consequently, amphotericin B lipid complex can be given at higher total doses. There is good evidence of reduced nephrotoxicity with the lipid complex formulations compared with conventional amphotericin B in some groups of immunosuppressed children and adults (Johansen 2002a; Blyth 2010). There are also some observational data to suggest lower toxicity in preterm infants (Weitkamp 1998; Juster-Reicher 2000; Adler-Shohet 2001). However, the lipid complex formulations are very much more expensive than conventional amphotericin B. In

current neonatal practice use is often restricted to infants who are intolerant of, or do not respond to, conventional amphotericin B.

Amphotericin B is highly protein bound and does not achieve good penetration into extracellular fluid spaces, including cerebrospinal fluid. Another drug is often used instead of, or in addition to, amphotericin B to treat preterm infants with suspected or confirmed fungal meningitis. The most commonly used additional agent is 5-fluorocytosine (flucytosine), a fluorinated pyrimidine anti-metabolite that competitively inhibits nucleic acid synthesis. 5-Fluorocytosine achieves very good penetration into the cerebrospinal fluid (Hill 1974). Since monotherapy is thought to increase the risk of the development of stable antifungal resistance, 5-fluorocytosine is usually prescribed with amphotericin B or another antifungal agent. Amphotericin B and 5-fluorocytosine are not antagonistic but the evidence for synergism is inconsistent and depends on the laboratory assessment method used (Keele 2001; Te Dorsthorst 2002). 5-Fluorocytosine is very well absorbed via the enteral route. Oral and intravenous preparations are available. The known side effects of 5-fluorocytosine include hepatic toxicity and transient neutropenia. Bone marrow suppression has also been reported (Vermes 2000).

Azoles

The second major class of antifungal agents available for treating preterm infants with invasive fungal infection is the azole group. These include triazoles (fluconazole, voriconazole) and imidazoles (miconazole, ketoconazole). These drugs bind preferentially to the fungal cytochromes P450 and interfere with ergosterol synthesis in the cell membrane. Azoles are well absorbed after enteral administration. A prolonged treatment course can therefore be given without the presence of an intravenous catheter. Some randomised controlled trials in immunosuppressed adults have reported that azole drugs are less toxic than conventional amphotericin B (Kontoyiannis 2001). However, Cochrane systematic reviews urge caution in interpreting and applying this evidence as the findings of several trials in this population are likely to have been biased by methodological and analysis flaws (Johansen 2002b; Jorgensen 2006).

There is little published experience of the use of imidazole drugs to treat invasive fungal infection in newborn infants (Tuck 1980; McDougall 1982). Triazoles, particularly fluconazole, are used more commonly in neonatal practice and appear to be a safe treatment for newborn infants. The most frequently reported side effect is transient elevation of plasma levels of creatinine or hepatic enzymes described in about 5% of infants treated with fluconazole (Huttova 1998). There are also rare important side effects such as Stevens-Johnson syndrome reported in other populations of patients (Gussenhoven 1991). Additionally, there is a potential risk of adverse effects as a result of drug interactions with medications that are prescribed for newborn infants, including cisapride, theophylline and thiazide diuretics (Neely 2001).

Echinocandins

Echinocandins (caspofungin, micafungin and anidulafungin) are newer antifungal agents that act by inhibiting 1,3- β -D-glucan synthase, a fungal enzyme necessary for cell wall synthesis (Sucher 2009; Chen 2011). Caspofungin and micafungin have been reported to be as effective as amphotericin B but with fewer adverse effects and drug interactions in treating adults with suspected or confirmed invasive fungal infection (Falagas

2007; Kuse 2007). However, there are few pharmacokinetic, safety or efficacy data relevant to children or infants (Heresi 2006a; Blyth 2010; VandenBussche 2010; Caudle 2012). The published experience in newborn infants consists mainly of case reports of treatment of fungal infections unresponsive or resistant to amphotericin B and fluconazole (Odio 2004; Natarajan 2005; Manzar 2006; Yalaz 2006; Smith 2007). Echinocandin resistance after prolonged use selects fungi with a mutation in the 1,3- β -D-glucan synthase gene has been described (Krogh-Madsen 2006; Laverdiere 2006; Baixench 2007). Reported side effects are generally mild and transient but acute hepatitis has been associated with micafungin use (King 2009).

Why it is important to do this review

Given the important differences in the epidemiology and pathogenesis of invasive fungal infection in newborn infants compared with older children and adults, and the potential for the choice of antifungal drug or drug preparation or combination to affect outcomes for newborn infants with invasive fungal infection, we reviewed the available evidence to determine if there are any implications for current practice or for future research (Blyth 2009).

OBJECTIVES

To assess the effect of treatment with one antifungal drug or drug combination or preparation versus another on mortality and morbidity in newborn infants with invasive fungal infection.

METHODS

Criteria for considering studies for this review

Types of studies

1. Controlled trials utilising either random or quasi-random patient allocation.
2. Cluster randomised trials, where the unit of randomisation is the neonatal nursery/unit/centre.

Types of participants

Newborn infants with confirmed or suspected invasive fungal infection. We defined "confirmed" invasive fungal infection as:

- culture of fungus from a sterile site, such as cerebrospinal fluid, blood, urine, bone or joint, peritoneum, pleural space. Blood cultures should have been obtained from peripheral sites, not from indwelling catheters. Urine samples should have been obtained from sterile urethral catheterisation or suprapubic aspiration of the bladder, not from indwelling catheters or from urine 'bag' samples (since organisms isolated from these may represent perineal contamination);
- findings on ophthalmological examination consistent with fungal ophthalmitis or retinitis;
- pathognomonic findings on renal ultrasound examination: 'renal fungal balls'.

We defined 'suspected' invasive fungal infection pragmatically as an individual clinician's choice to prescribe a systemic antifungal agent based on the clinical suspicion of invasive fungal infection, but in the absence of a confirmed diagnosis as described above.

We did not include trials of antifungal prophylaxis or trials where antifungal therapy was given to treat superficial mucosal or skin infection.

Types of interventions

One antifungal drug, drug combination or preparation versus another.

Types of outcome measures

Primary outcomes

1. Death (all cause) prior to hospital discharge.
2. Neurodevelopmental outcomes assessed beyond infancy (neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability, non-ambulant cerebral palsy, developmental delay) and cognitive and educational outcomes (intelligence quotient and/or indices of educational achievement measured using a validated tool including school examination results).

Secondary outcomes

1. Adverse reactions attributed to the antifungal agent that resulted in discontinuation of the therapy: abnormal hepatic function; abnormal renal function; gastrointestinal disturbance such as diarrhoea, feeding intolerance, or necrotising enterocolitis that results in cessation of enteral feeding; hypokalaemia; cardiac dysrhythmias; thrombophlebitis; rash (including Stevens-Johnson reactions); seizures.
2. Emergence of organisms resistant to antifungal agents as detected in infants enrolled in the study or, in cluster-randomised studies, on surveillance of other infants in the same unit in the study centre (including infants who are admitted to the unit following completion of the study).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2012), MEDLINE (1966 to March 2012), EMBASE (1980 to March 2012), and CINAHL (1982 to March 2012) using a combination of the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR LBW OR infan* OR neonat*] AND [Mycoses/ OR fung* OR candid* OR Candida albicans OR Antifungal Agents/ OR Triazoles/ OR azole OR fluconazole OR diflucan OR miconazole OR ketoconazole OR voriconazole OR ravuconazole OR posaconazole OR amphotericin B OR amphotericin B OR ABLC OR Ambisome OR Abelcet OR Amphocil OR 5-fluorocytosine OR 5FC OR flucytosine OR echinocandin OR caspofungin OR micafungin OR anidulafungin]. The search outputs were limited with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any language restriction.

We searched ClinicalTrials.gov and [Current Controlled Trials](#) for completed or ongoing trials.

Searching other resources

We examined the references in studies identified as potentially relevant. We also searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2011), the European Society for Paediatric Research (1995 to 2011), the UK Royal College of Paediatrics and Child Health (2000 to 2011) and the Perinatal Society of Australia and New Zealand (2000 to 2012). We considered trials reported only as abstracts to be eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

The two review authors screened the title and abstract of all studies identified by the above search strategy. We reassessed the full text of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until consensus was achieved.

Data extraction and management

We used a data collection form to aid extraction of relevant information from each included study. The two review authors extracted the data separately. We discussed any disagreements until consensus was achieved. We asked the investigators for further information if data from the trial reports were insufficient.

Assessment of risk of bias in included studies

We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of any included trials. Additional information from the trial authors was requested to clarify methodology and results as necessary. We evaluated and reported the following issues in the 'Risk of Bias' tables:

1. Sequence generation: we categorised the method used to generate the allocation sequence as:
 - a. low risk: any random process (e.g. random number table; computer random number generator);
 - b. high risk: any non-random process (e.g. odd or even date of birth; patient case-record number);
 - c. unclear.
2. Allocation concealment: we categorised the method used to conceal the allocation sequence as:
 - a. low risk: (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
 - b. high risk: open random allocation; unsealed or non-opaque envelopes, alternation; date of birth;
 - c. unclear.
3. Blinding: we assessed blinding of participants, clinicians and carers, and outcome assessors separately for different outcomes and categorised the methods as:
 - a. low risk;
 - b. high risk;
 - c. unclear.

4. Incomplete outcome data: we described the completeness of data including attrition and exclusions from the analysis for each outcome and any reasons for attrition or exclusion where reported. We assessed whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised completeness as:
 - a. low risk: < 20% missing data;
 - b. high risk: $\geq$ 20% missing data;
 - c. unclear.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and weighted mean difference (WMD) for continuous data, with respective 95% confidence intervals (CI). We determined the number needed to treat for benefit (NNTB) or harm (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis is the participating infant in individually randomised trials and the neonatal unit for cluster randomised trials.

Assessment of heterogeneity

We examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each RR analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If substantial heterogeneity ($I^2 > 50\%$) was detected, we explored the possible causes (e.g. differences in study design, participants, interventions or completeness of outcome assessments).

Assessment of reporting biases

If more than five trials were included in a meta-analysis, we planned to examine a funnel plot for asymmetry.

Data synthesis

We used the fixed-effect model in RevMan 5.1 for meta-analysis ([RevMan 2011](#)).

Subgroup analysis and investigation of heterogeneity

We pre-specified a subgroup analysis of outcomes for very preterm (< 32 weeks) or VLBW infants (< 1500 g).

RESULTS

Description of studies

We identified only one eligible trial ([Driessen 1996](#)). The trial, undertaken during 1992 to 1993 in two tertiary neonatal centres in South Africa, assessed the effect of treatment with fluconazole versus conventional amphotericin B (plus 5-fluorocytosine if meningitis suspected) in 24 newborn infants (22 of whom were preterm) with confirmed bloodstream fungal infection. Mortality was reported but the trial did not assess any long-term outcomes after hospital discharge. Data on adverse reactions to treatment

including gastrointestinal disturbance or thrombophlebitis were recorded throughout the study period.

Risk of bias in included studies

Randomisation was computer generated independently for the two centres and via a sealed envelope system for individual case allocation. Both preterm infants and term infants were eligible for inclusion in the trial and these groups were not randomised separately. There were not any statistically significant differences between treatment groups in infant characteristics at trial entry. Follow-up was complete with the exception of one infant in the fluconazole group who was excluded post-randomisation by the investigators as the infant did not have confirmed invasive fungal infection. The carers and assessors were blinded to randomisation. However, due to differences in the drug preparations, the carers and investigators were likely to be aware which drug each infant received.

Effects of interventions

Primary outcomes

1. Death prior to hospital discharge ([Analysis 1.1](#)): four of 12 infants in the fluconazole group died before discharge versus five of 11 in the amphotericin B group (RR 0.73; 95% CI 0.26 to 2.05; RD -0.12; 95% CI -0.52 to 0.28).

2. Neurodevelopmental outcomes not reported.

Secondary outcomes

1. This trial reported rates of adverse reactions. However, none of these resulted in discontinuation of treatment.

a. Hepatic function: there was no statistically significant difference in the plasma levels of the liver enzymes gamma-glutamyl transpeptidase, aspartate aminotransferase and alanine aminotransferase between the fluconazole and amphotericin groups at the end of treatment.

b. Thrombophlebitis ([Analysis 1.2](#)): one infant in the fluconazole group and five infants in the amphotericin group had evidence of thrombophlebitis resulting in skin abscesses (but not in discontinuation of treatment) (RR 0.18; 95% CI 0.03 to 1.33; RD -0.37; 95% CI -0.70 to -0.04).

c. Gastrointestinal disturbance: one infant in the fluconazole group had severe vomiting. However, this infant also had a disorder of branch chain amino acid metabolism.

2. Emergence of antifungal resistance is not reported in this study.

Subgroup analysis

We were unable to undertake subgroup analysis of very preterm or VLBW infants.

DISCUSSION

Summary of main results

We identified only one eligible study ([Driessen 1996](#)). This small trial compared fluconazole with conventional amphotericin B as

treatment for newborn infants with confirmed invasive fungal infection. Although the study was of good methodological quality, the trial was too small (total of 24 infants) to allow meaningful conclusions to be drawn.

We did not find any studies that compared the use of conventional amphotericin B with liposomal amphotericin B preparations.

We did not find any trials that assessed the effect of treatment with other azoles or echinocandins.

Overall completeness and applicability of evidence

Our pre-specified outcomes did not include any specific measure of convenience of drug administration or of the cost of the treatment course although these may be related to the incidences of side effects that result in discontinuation of therapy. In the included study, the incidence of thrombophlebitis was borderline statistically significantly lower in the group treated with fluconazole compared to amphotericin B, but this complication did not result in discontinuation of treatment. There were no other instances of adverse events resulting in discontinuation of therapy. The trial also found that there were no statistically significant differences in duration of treatment, days in hospital after enrolment to the study or duration of need for a central venous line. However, the mean duration of intravenous antifungal therapy was statistically significantly lower for the fluconazole group (which is well absorbed orally and was prescribed enterally for part of the treatment course) compared with amphotericin B.

AUTHORS' CONCLUSIONS

Implications for practice

There are insufficient data to determine whether treatment with different antifungal drugs or drug combinations affects mortality and adverse neurodevelopmental outcomes in newborn infants with suspected or confirmed invasive fungal infection. In the absence of these data, the choice of therapy may be affected by other considerations such as the cost of the treatment course and the convenience of use.

Implications for research

Very large pragmatic randomised controlled trials would be required to determine if any of the newer antifungal drugs or preparations reduce mortality and adverse neurodevelopmental outcomes compared with conventional amphotericin B. Trials should also address the effect of increased use of particular agents on the emergence of organisms resistant to antifungal drugs. This may necessitate the use of a cluster-randomised trial design, with the neonatal centre as the unit of randomisation. Further research may also determine the relative convenience and cost effectiveness of the available drugs. For example, drugs that are well absorbed orally may be more convenient and cost effective in practice.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Driessen 1996

Methods	Randomised controlled trial
Participants	24 newborn (22 preterm) infants with invasive fungal infection, aged less than 3 months old June 1992 to June 1993 in 2 tertiary neonatal centres in Witwatersrand, South Africa
Interventions	Fluconazole 10 mg/kg intravenously or orally then 5 mg/kg once daily (n = 13), versus amphotericin B 1 mg/kg/day infused intravenously over 4 to 6 hours (n = 11) Treatment continued until fungal cultures negative for 1 week and no laboratory evidence of infection
Outcomes	Death before hospital discharge Haematological, renal, hepatic functions; monitored weekly Adverse reactions, convenience of use
Notes	24 infants were recruited to the study but 1 infant in the fluconazole group was excluded post-randomisation by the investigators as the infant did not have confirmed invasive fungal infection
Risk of bias	

Driessen 1996 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Computer-generated random sequence independently for the 2 centres and allocation using a sealed envelope system
Blinding (performance bias and detection bias) All outcomes	High risk	Due to differences in the drug preparations, the carers and investigators were likely to be aware which drug each infant received
Blinding of outcome assessment (detection bias) All outcomes	High risk	Due to differences in the drug preparations, the carers and investigators were likely to be aware which drug each infant received
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up was complete with the exception of 1 infant in the fluconazole group who was excluded post-randomisation by the investigators as the infant did not have confirmed invasive fungal infection
Selective reporting (reporting bias)	Low risk	Follow-up was complete with the exception of 1 infant in the fluconazole group who was excluded post-randomisation by the investigators as the infant did not have confirmed invasive fungal infection

DATA AND ANALYSES
Comparison 1. Fluconazole versus amphotericin B

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality before hospital discharge	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.26, 2.05]
2 Presence of thrombophlebitis	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.03, 1.33]

Analysis 1.1. Comparison 1 Fluconazole versus amphotericin B, Outcome 1 Mortality before hospital discharge.

Analysis 1.2. Comparison 1 Fluconazole versus amphotericin B, Outcome 2 Presence of thrombophlebitis.

WHAT'S NEW

Date	Event	Description
17 April 2012	New citation required but conclusions have not changed	The search was revised and updated in April 2012. Expanded population to all newborn infants (previously preterm infants). No new trials for inclusion were identified.
3 April 2012	New search has been performed	This updates the review "Antifungal therapy for newborn infants with invasive fungal infection" (Cleriheuw 2004).

CONTRIBUTIONS OF AUTHORS

The first review author (LC) screened the title and abstract of all studies identified by the above search strategy. Both review authors re-screened the full text of the report of each study identified as of potential relevance. The review authors resolved any disagreements by discussion until consensus was achieved. Both review authors used a data collection form to aid extraction of relevant information and data from each included study. Each review author extracted the data separately, compared data and resolved differences by consensus. Both review authors contributed to the analysis and interpretation of the data, and the completion of the review.

DECLARATIONS OF INTEREST

None.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the [Background](#) section and expanded and re-run the [Electronic searches](#). We have also expanded the [Types of participants](#) from preterm infants to all newborn infants (with appropriate [Subgroup analysis and investigation of heterogeneity](#) specified).

INDEX TERMS

Medical Subject Headings (MeSH)

Amphotericin B [therapeutic use]; Antifungal Agents [*therapeutic use]; Fluconazole [therapeutic use]; Flucytosine [therapeutic use]; Infant, Premature; Infant, Premature, Diseases [*drug therapy]; Mycoses [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn