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MINIREVIEW

Antifungal Agents in Neonatal Systemic Candidiasis

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Neonatal systemic candidiasis is increasingly being recognized as a cause of septicemia in the neonatal intensive care unit (2, 19, 26, 36, 59). Predisposing factors for candidemia and subsequently invasive infections include prematurity, prolonged exposure to broad-spectrum antibiotics, the use of intravenous fat emulsions, the presence of necrotizing enterocolitis, prolonged intravascular catheterization, and tracheal intubation (33, 49, 50, 51, 63). Moreover, the immune functions of the newborn, especially in the preterm infant, are suboptimal, manifested as a decreased T-cell and granulocyte function (6, 22, 65). Additionally, it has been shown that lung macrophages of newborns have reduced anti-*Candida* activity (16). Infection is preceded generally by colonization of the gastrointestinal tract and the skin shortly after delivery (1, 27). Clinical evidence suggests that heavy colonization at multiple sites is a predisposing factor for clinical disease (27, 41), although this is still controversial (40). Most fungal infections in newborns are caused by *Candida albicans*, *Candida parapsilosis*, and more rarely, *Candida tropicalis* (1, 20, 42, 48).

The symptoms of systemic candidal infection in the newborn are not specific. In several studies deterioration of respiratory function and apnea were the most common presenting signs, occurring in 70% of infants (2, 10, 26). Temperature instability, irritability, abdominal distension, carbohydrate intolerance, rash, and lethargy were also commonly observed. Similar symptoms are noted in newborns with bacterial infections, which occur frequently or coincidentally with systemic candidiasis. Therefore, most fungemic newborns are presumptively treated for bacterial infection. Since the signs, symptoms, and results of hematologic studies for infants suspected of having candidiasis are not specific, positive cultures are the mainstay in the diagnosis of invasive candidiasis. However, in newborn patients most antifungal therapy is started when fungal elements are seen on Gram stain or yeasts are isolated from some body fluid. On occasion it is even begun empirically or on the basis of the presence of a suggestive rash. Amphotericin B with or without flucytosine is still the treatment of choice for newborns with systemic candidiasis. However, since the introduction of ketoconazole in 1981, fluconazole in 1990, and intraconazole in 1992, these antifungal azoles, which unlike amphotericin B can be given orally, there has been a tendency to use these drugs as alternative therapies. Physicians have been influenced by the efficacy, safety, and ease of the administration of the azoles, despite the lack of direct comparisons of the efficacies of these drugs and amphotericin B. Our purpose here is to present an overview of the available pharmacokinetic data for amphotericin B, flucytosine, and this new group of azole drugs in the newborn. Dosage recommendations, recommendations for dosage adjustments in the face of organ system failure, and recommendations for monitoring toxicity will be suggested.

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AMPHOTERICIN B

The antifungal activity of amphotericin B is related to its binding with ergosterol and other sterols of the fungal cell membrane which produces a disruption of its integrity and transport characteristics in susceptible organisms, resulting in the loss of intracellular potassium (3, 32). Resistance can develop very slowly and may result from a decrease in the concentration of ergosterol in the fungal cell membrane (32).

In 1984 Baley et al. (2) reported that 7 of 10 infants receiving amphotericin B for systemic fungal infections had severe nephrotoxicity with oliguria or anuria and marked increases in blood urea nitrogen and creatinine. However, several infants had confounding factors such as prior poor renal function and multiple drug therapies. The nephrotoxicity was seen in one infant after administration of the first 0.25 mg/kg of body weight, whereas the others required an average cumulative dose of 6.5 mg/kg before renal side effects occurred. The deaths of six of these infants were attributed, in part, to amphotericin B-induced nephrotoxicity. Since that report, the pharmacokinetics of amphotericin B in newborns have been studied and most of the treated infants have had more favorable outcomes. In contrast to adults, who experience fever, chills, nausea, and vomiting, infants tolerate infusion well (18, 26, 45, 62). The major side effects are transient nephrotoxicity, hepatotoxicity, and bone marrow suppression. Amphotericin B specifically suppresses production of erythrocytes because of inhibition of erythropoietin production (35). In infants and children it has been shown that after 1 week of treatment the creatinine level rose but reverted to the baseline level by the end of treatment (54). There have also been reports of inadvertent overdosing of infants (29, 38). Koren et al. (29) described an infant who received 50 times the normal dose of amphotericin B on three separate occasions. Except for a mild persistent elevation of γ-glutaryltransferase levels, the infant tolerated the massive overdose without any other measurable difficulty and remained well later on. There appears to be a high degree of variability in peak levels in serum, elimination half-life in serum and volume of distribution of amphotericin B among infants (Table 1) (3, 54, 62). The data from different investigators cannot easily be compared because of different dosing schedules and assays of drug concentrations. Most studies document a longer elimination half-life in serum in smaller infants, who appeared to accumulate the drug. Koren et al. (30) speculated that maturation of the hepatic metabolism of amphotericin B takes place in infancy and childhood. The

TABLE 1. Pharmacokinetics of AmB[a]

Reference	Dosage (mg/kg/24 h)	Dose (mg/kg)	Peak level (mg/liter)	Trough level (mg/liter)	Half-life (h)	Vol. of distribution (liters/kg)	Clearance (ml/min/1.73 m^2)	Clearance (ml/min/kg)
Baley et al. (2)	0.5		0.96 (0.5–4.0)		14.8 (5–82)	1.5 (0.1–17.5)	18.0 (7.7–72.3)	
Starke et al. (54)	1.0		0.31–1.22	0.08–0.32	7.46–62.5	1.5–5.4		0.78–3.87
Ward et al. (62)		0.5–1.0	0.20–0.65	0.20				

[a] Values are expressed as mean (range).

practical implication of the age-dependent changes in the half-life in serum is that it may take significantly longer periods to achieve steady state in the younger infant (30).

In contrast to adults, in whom the concentrations of amphotericin B in cerebrospinal fluid may be only 2 to 4% of those in serum (43), in five infants in whom concentrations of amphotericin B in cerebrospinal fluid were studied, the levels were 40 to 90% of those in serum (3). This may explain why infants with fungal meningitis have similar outcomes whether they are treated with amphotericin B alone or with flucytosine. Assays of amphotericin B in joint fluid also revealed concentrations similar to those in serum (54). Urinary excretion is less than 5% of the concentration in serum (66). Therapeutic dosing of amphotericin B is started at 0.25 mg/kg. This is usually followed by daily increases of 0.25 mg/kg to achieve a daily dose of from 0.5 to 1.0 mg/kg. For patients with severe disease, dose increases have been used every 12 h, and these have been well tolerated. Although 0.5 mg/kg may be efficacious (2, 3, 26), daily doses of up to 1.5 mg/kg have been safely given (10). The optimal dose and duration of amphotericin B therapy for systemic candidiasis in adults are unknown, although the drug has been available for more than 30 years. Also, in infants and children the proposed duration of therapy is rather variable. Sánchez et al. (45) advise a total dose of 10 to 20 mg of amphotericin B per kg for most infants with uncomplicated catheter-associated candidemia, whereas Butler et al. (11) recommend a minimum total dose of 25 mg/kg in infants with disseminated candidal disease. At present, therapy should therefore be individualized on the basis of the type of infection, the immune functions of the newborn, and the newborn's response while on therapy. Careful monitoring of renal function, blood counts, and electrolytes is required, and adjustments to the drug dose and the dosing interval are based on studies of those parameters.

An interesting new development for the near future is the administration of amphotericin B in lipid complexes or liposomes. The incorporation of amphotericin B in liposomes resulted in decreased toxicity and enhanced therapeutic efficacy against several infections in animals (37). The role of liposomal amphotericin B in the newborn has still to be elucidated (31).

FLUCYTOSINE

Flucytosine is a fluorine analog of cytosine, a normal body constituent. After deamination in the fungal cell, the drug is transformed to 5-fluorouracil, which acts as an inactive pyrimidine substitute and which also inhibits thymidylate synthetase. These two mechanisms interfere with DNA synthesis and cell growth (32). The development of secondary resistance has been demonstrated in vitro and can occur during therapy, especially when the drug is used on its own (2, 14, 32). Flucytosine is used as adjunctive therapy with amphotericin B, although the need for it has recently been debated (11). At present there are few clinical data on the efficacy of flucytosine alone or in combination with amphotericin B for the treatment of neonatal systemic candidiasis. Furthermore, the use of flucytosine, which is available only for oral administration, is limited because preterm infants are often unable to tolerate oral medications.

Side effects occur in about 5% of adult patients and generally involve the bone marrow, liver, and gastrointestinal tract. Gastrointestinal and hepatic toxicities apparently are not related to the concentrations of flucytosine in serum, whereas myelosuppression does correlate with the concentrations in serum. The most common gastrointestinal toxicities are nausea, vomiting, and diarrhea. Hepatic toxicities consist of elevated transaminase and alkaline phosphatase levels in serum, which are reversible. Rarely, patients develop patchy hepatic necrosis. Flucytosine toxicity occurred in 62% of 37 patients in whom the concentrations of drug in serum were >100 mg/liter for 2 or more weeks but in only 31% of 48 patients in whom the concentrations in serum were <100 mg/liter (53). Myelosuppression is the toxicity of the greatest concern and may be manifested as anemia, leukopenia, and thrombocytopenia. Presumably, this toxicity is due to the conversion of flucytosine to 5-fluorouracil in the gastrointestinal tract. If the concentration of flucytosine in serum exceeds 100 mg/liter, the concentration of 5-fluorouracil in serum likely exceeds 1 mg/liter, which is within its therapeutic range (17). The hematological side effects have been related to concentrations of flucytosine in serum of greater than 100 mg/liter (28). Flucytosine is not directly nephrotoxic, although approximately 90% of the drug is excreted unchanged in the urine of adults. The elimination rate constant is directly related to glomerular filtration, so that potentially dangerous levels may occur if glomerular filtration is impaired (62). Several studies did not show any side effects of flucytosine in infants (12, 18, 26, 62). Baley et al. (3) reported that in two of seven autopsied infants, hepatic necrosis was present.

There appears to be a high degree of variability in peak levels in serum, elimination half-life in serum, and volume of distribution of flucytosine among the studied infants (Table 2) (3, 26, 50, 62). The data from different investigators cannot easily be compared because of different dosing schedules, different assays of drug concentrations, and both parenteral or enteral administration of flucytosine. Moreover, only one study provided us with the full pharmacokinetic parameters of flucytosine (3). Baley et al. (3) showed that the elimination half-lives in the sera of 12 infants were variable, ranging from 3.4 to 34.1 h, with a median of 7.5 h, which is twice that in the sera of adults (13). The penetration of flucytosine into the cerebrospinal fluid of newborns is excellent (Table 3) (26, 50).

As with amphotericin B, the optimal dose and duration of treatment with flucytosine are unknown. In the reports reviewed here, the dosage has ranged from 50 to 200 mg/kg/24 h, and the duration of treatment has ranged from 10 to 120 days. Baley et al. (3) recommend a dosing interval of 24 h in newborns rather than the 6-h interval recommended for adults, because they showed that the median half-life of flucytosine in the newborns studied was prolonged compared with the half-life found in adults (3).

TABLE 2. Pharmacokinetics of flucytosine[a]

Reference	Dosages (mg/kg/24 h)	Dose (mg/kg)	Peak level (mg/liter)	Trough level (mg/liter)	Concn in serum at steady state (mg/liter)	Half-life (h)	Vol of distribution at steady state (liters/kg)	Clearance (ml/min/1.73 m^2)	Clearance (ml/min/kg)
Ward et al. (62)	40		25	8					
	80		37	27					
Johnson et al. (26)		25			57 ± 10				1.2
Smith and Congdon (50)	100–200		50–100	25–100					
	25		19.6						
Baley et al. (2)	50		27.7 (11–44)			7.4 (3.4–34.1)	1.1 (0.1–2.0)	34.2 (8.72–49.2)	
	100		83.9						

[a] Values are expressed as median (range).

Careful monitoring of transaminase and alkaline phosphatase levels in serum, renal function, and blood counts is required, and adjustments to the drug dose and the dosing interval are based on studies of these parameters. Additionally, because the hematological side effects have been associated with concentrations of flucytosine in serum greater than 100 mg/liter, monitoring of flucytosine levels is indicated to appropriately adjust the dosing schedule.

KETOCONAZOLE

Ketoconazole is an imidazole derivative. The antifungal activity of ketoconazole is related to its inhibition of 14-α-demethylation of lanosterol by binding to one of the cytochrome enzymes. This impairs the synthesis of ergosterol and interferes with the formation of other cell membrane lipids (32). The development of clinically important resistance to ketoconazole, even after prolonged courses of therapy, is unknown.

The use of ketoconazole, which is available only for oral administration, is limited because preterm infants are often unable to tolerate oral medications. Furthermore, ketoconazole is a weak base and requires an acid environment for optimal solubilization and absorption. Side effects occur in about 2 to 10% of adult patients and generally involve the liver and the gastrointestinal tract. Although most patients with ketoconazole-induced elevations in aminotransferase concentrations in plasma are asymptomatic, ketoconazole may cause clinically important and even fatal hepatitis (34). Moreover, ketoconazole may reversibly inhibit the synthesis of testosterone (and therefore estradiol) and cortisol, resulting in a variety of endocrine disturbances, including gynecomastia, oligospermia, loss of libido, impotence, menstrual irregularities, and very rarely, adrenal insufficiency (44, 52). Most side effects are dose related. Side effects in newborns have not been reported.

TABLE 3. Drug concentrations in cerebrospinal fluid

Reference	Drug[a]	Dosage (mg/kg/24 h)	Concn (mg/liter)
Baley et al. (2)	AmB	0.5	—[b]
Johnson et al. (26)	5FC	25	43
Smith and Congdon (50)	5FC	120–150	20–67
Bardare et al. (4)	KCZ		ND[c]–0.03
Cruciani et al. (15)	FLU	6	6.6–8.6

[a] AmB, amphotericin B; 5FC, flucytosine; KCZ, ketoconazole; FLU, fluconazole.

[b] —, the concentration was determined to be 40 to 90% of the concentration in serum.

[c] ND, not detectable.

The data from different investigators cannot easily be compared because of the different ages, different dosing schedules, and different assays of drug concentrations and the use of solutions, tablets, and crushed tablets (Table 4) (4, 57). Bardare et al. (4) reported the pharmacokinetics of ketoconazole treatment in 26 children (ages, 5 months to 14 years). Ketoconazole was given as a suspension or as tablets. Double peaks were observed in two patients receiving ketoconazole tablets, probably because of enterohepatic circulation or delayed absorption. In a study by Ginsburg et al. (23) a comparison between the pharmacokinetics of ketoconazole after administration as a commercially prepared suspension or as a crushed tablet in applesauce in 12 children from 2 to 12.5 years of age was made (23). The mean peak concentration of ketoconazole in plasma and areas under the serum concentration-time curves were approximately twofold higher for those receiving the suspension than for those receiving the powder. They found a considerable variation in concentrations in plasma. The half-life in plasma tended to be longer after administration of crushed tablets than after administration of the suspension; however, this difference was not significant. Of the patients receiving the suspension, peak concentrations in plasma were 4 μg/ml or greater in 67% of them.

In the study of Bardare et al. (4), 26 children with candidiasis were treated with ketoconazole. A total of 73% of the children were cured and 11.5% improved. Failure was observed in one patient who was being treated with cimetidine at the same time (4). Van den Anker et al. (58) showed that with dosages of 3 and 6 mg of ketoconazole per kg/day given orally as a single drug to preterm infants, measurable concentrations in serum were not reached. They suggested that a possible explanation is that absorption of ketoconazole is prevented by a combination of low or absent gastric acid secretion, continuous gavage feeding, and the high buffering capacity of milk. In a supplementary study of van den Anker et al. (57) the relation between gastric pH and the bioavailability of ketoconazole was studied with eight preterm infants who received a single oral dose of 10 mg of ketoconazole per kg. In seven of the eight infants, appropriate absorption of ketoconazole was demonstrated. The conclusion of that study was that ketoconazole is absorbed (pH dependent) from the gastrointestinal tract in preterm infants. Bardare et al. (4) concluded that a dosage of at least 8 mg/kg/day is needed to achieve acceptable concentrations in serum and definite cures, although Bardare et al. (4) gave ketoconazole as a suspension. They found, however, that the same dosage was suitable for children receiving tablets, provided

TABLE 4. Pharmacokinetics of ketoconazole

Reference (dosage formulation)	Dose (mg/kg)	Peak level (mg/liter)	Concn in serum (mg/liter) at:			Half-life (h)	AUC (μg · h/ml) at[a]:		
			8 h	12 h	24 h		0–8 h	0–12 h	0–24 h
Bardare et al. (4)									
Suspension	3	0.5	ND[b]			0.75	1.15		
	10	2.04	0.64			3.78	9.51		
Tablets									
One daily dose	8.70	6.30	1.81	0.72	0.04	2.38		36.67	40.67
Two daily doses	9.61	3.46	0.35	0.10		2.57		13.64	
Van den Anker et al. (57)	10	1.41							8.80

[a] AUC, area under the concentration-time curve.
[b] ND, not detectable.

that an antacid drug was not administered simultaneously (4). There is no penetration of ketoconazole into the cerebrospinal fluid of infants aged between 5 months and 14 years (4). Data on the concentration of ketoconazole in the cerebrospinal fluid of newborn infants are completely lacking.

The optimal dose and duration of treatment with ketoconazole are unknown. Because of the pH-dependent absorption of ketoconazole, a low gastric pH must be guaranteed if ketoconazole is used. Derived from the reviewed literature, a starting dose of 8 to 10 mg of ketoconazole per kg would therefore be appropriate. Because little ketoconazole is excreted in the urine, the doses need not be changed in patients with renal impairment.

Careful monitoring of aminotransferase concentrations in plasma is obligatory. Therapy with ketoconazole should always be discontinued for infants who have symptomatic hepatitis or laboratory evidence of progressive or persistent hepatic dysfunction. Changes in steroidogenesis should be searched for.

FLUCONAZOLE

Fluconazole is a bistriazole antifungal agent. The mechanism of action of fluconazole is by inhibition of fungal ergosterol synthesis.

Until recently, the development of clinically important resistance to fluconazole was rare (21, 39). However, treatment failures are increasing among patients infected with the human immunodeficiency virus who are receiving intermittent or continuous fluconazole therapy (46). Fluconazole is available as both an oral and an intravenous formulation. The absorption of oral fluconazole is not altered by the presence of food or gastric acidity.

Side effects occur in about 1 to 7% of adult patients and generally involve the liver and the gastrointestinal tract. Asymptomatic elevations of aminotransferase levels in plasma and hepatitis (rare) are seen (24). No effects of fluconazole on steroidogenesis have been reported. Until now side effects in newborn infants were not reported (9).

The pharmacokinetics of fluconazole were determined by Saxen et al. (47) (Table 5), who treated 12 preterm infants prophylactically with fluconazole in an attempt to eradicate a *C. parapsilosis* outbreak on their neonatal intensive care unit. Up to five doses of 6 mg of fluconazole per kg were administered intravenously every 72 h during the first 2 weeks of life. A remarkable finding was the doubling of the mean total clearance corrected for body weight between dose 1 and dose 3 and a further increase by approximately 58% between dose 3 and dose 5. The clearance increased with postnatal age, whether or not it was corrected for body weight, but not with postconceptional age. This is probably an expression not only of renal functional development but also of clinical improvement. The other pharmacokinetic variables did not correlate with postnatal or postconceptional age. Wiest et al. (64) report a case of systemic candidiasis in a preterm infant who was treated with fluconazole after treatment with amphotericin B and flucytosine failed. They determined the concentrations of fluconazole in serum and used a first-order, one-compartment model to determine the pharmacokinetic parameters for fluconazole. These parameters indicate a larger apparent volume of distribution and a longer half-life compared with those in adults, which was also found by Saxen et al. (47). According to Bergman et al. (7), the concentrations of fluconazole in plasma after oral administration are sufficient. However, we like to stress that we need carefully designed pharmacokinetic and pharmacodynamic studies with newborn infants before we can conclude that certain concentrations in serum are sufficient.

In an evaluation of fluconazole in the treatment of candidiasis in 24 immunocompromised children (median age, 6 years;

TABLE 5. Pharmacokinetics of fluconazole

Reference	Dosage (mg/kg/24 h)	Dose (mg/kg)	Peak level (mg/liter)	Trough level (mg/liter)	Half-life (h)	Vol. of distribution (liters/kg)	Clearance (ml/min/kg)
Wiest et al. (64)	6		10.30	6.98	37.4	1.2	0.33
Bergman et al. (7)		20	11.1	6.8			
Saxen et al. (47)							
Dose 1		6	5.5	2.6	88.6	1.18	0.18
Dose 3		6	12.8	4.3	67.5	1.84	0.33
Dose 5		6	10.0	2.9	55.2	2.25	0.52

age range, 13 days to 14 years), only 2 patients treated with the standard dosages developed mild hepatotoxicity (61). Viscoli et al. (61) demonstrated that a total of 34 treatment courses in 24 patients resulted in 30 clinical and microbiological cures (88%). Four episodes (12%) did not respond to treatment, and improvement was obtained with amphotericin B in one patient in combination with flucytosine. Relapse occurred in 10 of the 30 responding episodes (33%) after the discontinuation of treatment. Relapses were due to persistence of the predisposing conditions. In the other articles reviewed here, treatment with fluconazole was successful (7, 9, 15, 60, 64). The concentrations of fluconazole in cerebrospinal fluid were determined by Cruciani et al. (Table 3) (15). When fluconazole is used in the treatment of systemic candidiasis in neonates, it is administered at a dosage of 5 or 6 mg/kg/day either orally or intravenously (7, 9, 15, 60, 64). The length of treatment ranges from 8 days to 3 months. Saxen et al. (47) used a dosing schedule of 6 mg/kg every 3 days, which resulted in the presumed desired mean trough concentrations of fluconazole in serum during the first week of life. However, the resulting decrease in half-life and trough concentrations in serum during the second week of life, when the same dosage was continued, led them to suggest that fluconazole should be administered every 2 days after the first week of life. Their experience obtained after the study period with the use of 6 mg of fluconazole per kg daily for 26 very low birth weight infants suggests that even higher doses of fluconazole can be used. Because approximately 80% of an administered dose of fluconazole is excreted unchanged in the urine, the dose should be reduced in patients with an impaired glomerular filtration rate. Careful monitoring of aminotransferase levels in plasma is indicated.

ITRACONAZOLE

Itraconazole is a triazole derivative. The mechanisms of action are basically similar to those of the other azoles. It inhibits the synthesis of ergosterol, and its use results in the simultaneous accumulation of 14-α-methysterols. Its effect seems to be acquired principally through inhibition of the cytochrome P-450 system (32). The development of clinically important resistance to itraconazole is unknown. The use of itraconazole, available only for oral administration, is limited because preterm infants are often unable to tolerate oral medications. Furthermore, itraconazole is a weak base and requires an acid environment for optimal solubilization and absorption. The bioavailability of itraconazole is two to three times higher when it is taken with food than when it is taken on an empty stomach (5). The bioavailability of itraconazole is increased when it is administered in hydroxypropyl-β-cyclodextrin, a cyclic oligosaccharide carrier molecule that increases the solubility of lipophilic compounds in aqueous solutions (25).

Side effects occur in about 1 to 5% of adult patients and generally involve the liver and gastrointestinal tract. Asymptomatic elevations of aminotransferase levels in plasma and hepatitis (rare) are seen. No effects on steroidogenesis have been reported. Side effects in newborn infants have not been reported.

There is only one report of itraconazole levels in sera of preterm neonates (56). Trough and peak levels of itraconazole in serum were measured in six preterm neonates 48 h after initiating therapy with itraconazole at 5 mg/kg/24 h and were found to be 276 ± 41 and 85 ± 18 μg/liter, respectively. A total of five doses were administered. The area under the serum concentration-time curve from 0 to 24 h could be determined in four neonates and was found to be 5.138 ± 1.188 μg · h/liter.

Two reports (8, 55) describe three preterm infants with disseminated candidiasis who were treated with itraconazole. All three infants made a complete recovery (8, 55). In two studies (54, 55) a dosage of 5 mg/kg/24 h was given orally. One study showed that itraconazole given at 5 mg/kg/24 h is well absorbed and that the recommended levels are reached in preterm neonates of less than 32 weeks of gestational age (56). In the other study a dosage of 10 mg/kg/day given orally was used in both children (8). Treatment was given for 3 to 4 weeks (8, 55).

Because little itraconazole is excreted in the urine, the doses need not be changed for patients with renal impairment. Careful monitoring of aminotransferase levels in plasma is indicated.

PERSPECTIVE

A more rapid and precise diagnosis of neonatal systemic candidiasis and an optimal individualized treatment strategy for the newborn with invasive candidiasis are major challenges for clinicians and researchers in the field. The use of nucleotide probes specific for *Candida* species and DNA amplification procedures such as PCR probably will allow a rapid and precise diagnosis of neonatal systemic candidiasis in the near future. Determination of which drug should be used to treat an infection with a specific pathogen in a specific newborn still awaits a lot of research. At present in vitro susceptibility testing of antifungal agents against fungal organisms is of questionable value because of the limited correlation of the results with the clinical response. Moreover, comparisons of MICs from laboratory to laboratory and from study to study should be interpreted with caution because the results are influenced by a variety of factors, including the growth medium, pH, temperature, and size of the inoculum. Because of the lack of standardized in vitro test systems, susceptibility testing of fungal isolates against antifungal drugs should not be done routinely in clinical microbiology laboratories but should be done only in selected reference or research settings. Therefore, at present the laboratory cannot help us to determine which drug should be used in a specific patient. This also accounts for the fact that minimal fungicidal concentrations and MICs for fungal isolates are not used commonly in the neonatal setting, indicating that at present the minimal fungicidal concentration and MIC have no value as clinical tools.

In our introduction we stated that amphotericin B with or without flucytosine was still the treatment of choice for newborns with systemic candidiasis. On the basis of the information in the literature presented here, amphotericin B remains the drug of choice for the treatment of systemic candidiasis, despite the need for prolonged intravenous cannulation and the potential for serious toxicity. However, newborns on amphotericin B therapy should concurrently receive recombinant erythropoietin to overcome the amphotericin B-induced inhibition of erythropoietin production. We recommend a starting dose of 0.25 to 0.5 mg/kg and, subsequently, a rapid increase of 0.25 to 0.5 mg/kg every 12 to 24 h until the upper limit of 1.0 to 1.5 mg/kg has been reached. Careful monitoring should be performed, as indicated above. We do not recommend the use of flucytosine because there are no clinical data on the efficacy of flucytosine alone or in combination with amphotericin B for the treatment of systemic candidiasis, and there is a rapid emergence of resistant *Candida* strains after flucytosine treatment.

What is the potential role of the new azole drugs (ketoconazole, fluconazole, and itraconazole)? Among these three, fluconazole has the most attractive profile, including the capacity to produce high concentrations in cerebrospinal fluid and good oral absorption unaltered by the presence of food or gastric

acidity. A potential disadvantage is the emergence of resistance. Ketoconazole is less well tolerated than either fluconazole or itraconazole and is associated with more clinically important toxic effects, including hepatitis and inhibition of steroid hormone synthesis. However, ketoconazole is much cheaper than fluconazole and itraconazole. Itraconazole has fewer potential side effects, but it has unreliable oral absorption. The use of hydroxypropyl-β-cyclodextrin will probably overcome this unreliable oral absorption. We like to stress that in preterm infants the use of all three drugs is limited because they are often unable to tolerate oral medications.

At present fluconazole, which is available as both an oral and an intravenous formulation and which has fewer potential side effects than amphotericin B, must be the antifungal agent that should be studied in comparative randomized multicenter trials with amphotericin B to obtain insight into the efficacy and toxicity of this azole drug. We recommend, on the basis of the experience of Saxen et al. (47), a starting dosage of 6 mg/kg every 2 days during the first 2 weeks after birth and 6 mg/kg every day later on.

Careful monitoring as indicated before should be performed.

Finally, in addition to the potential use of these new azole drugs in the treatment of neonatal systemic candidiasis, the roles of passive immunotherapy and gamma interferon therapy should be elucidated.

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