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Antifungals in Systemic Neonatal Candidiasis

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Abstract

Fungal infections are common in the newborn period, especially among premature neonates, and are responsible for considerable morbidity and mortality. Currently, three classes of antifungals are commonly used in the treatment of systemic fungal infections in neonates: the polyene macrolides (e.g. amphotericin B [deoxycholate and lipid preparations]); the azoles (e.g. fluconazole); and the fluorinated pyrimidines (e.g. flucytosine). The echinocandins (e.g. caspofungin and micafungin) are a newer class of antifungals which shows promise in this population.

The available kinetic data on amphotericin B deoxycholate in neonates are derived from very small studies and exhibit considerable variability. There are no kinetic data available for the use of lipid preparations in this population and, again, much has been inferred from adult studies. The information available for flucytosine is also limited but appears similar to what is observed in adults. Fluconazole has the most neonatal pharmacokinetic data, which show slightly less variability than the other antifungals. Genomic factors which affect the metabol-

ism of amphotericin B and fluconazole may explain some of the observed variability.

Most of the data for the efficacy of antifungal drugs in neonates are derived from retrospective studies and case reports. The data for amphotericin B deoxycholate and flucytosine are limited. There are more data for the liposomal and lipid complex preparations of amphotericin B and for fluconazole in this population. These support the use of these drugs in neonates, but because of their largely noncomparative nature they can not define the optimal dosage or duration of therapy.

Amphotericin B deoxycholate is primarily nephrotoxic. It also induces electrolyte abnormalities and is to a lesser degree cardiotoxic. This toxicity in neonates appears similar to published data in older children and adults. While the lipid preparations of amphotericin B owe their existence to a presumed decrease in toxicity, the observed toxicity in neonates appears to be equal to that seen with the deoxycholate, although it should be noted that the lipid preparations are usually given at much higher dosages. Fluconazole toxicity appears to be milder and less frequent in this population than is seen with amphotericin B.

In the final analysis, we do not have sufficient data to define the pharmacokinetic profiles, optimal dose or duration of therapy, or toxicity for any of these compounds in neonates. Further studies are necessary if the optimisation of antifungal therapy in this population is to continue.

Fungal infections are common in the neonatal period, especially among premature neonates, where 2–4.5% of those weighing <1500g at birth will have an invasive fungal infection that may be fatal in up to 25–50% of cases.[1-12] Risk factors for the development of invasive fungal infections include immature immune function (specifically in phagocytic and T-cell defences), aggressive neonatal intensive care techniques, and protracted courses of broad-spectrum antimicrobials.[3,5,7,13-17] *Candida albicans* is the most common pathogen in invasive fungal infections in neonates, although *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. lusitaniae* cause clinically indistinguishable infections.[4,13,18] While many preterm infants are colonised with *Candida* spp. during delivery, with skin colonisation preceding systemic infection, other infections are hospital acquired or are the result of common-source outbreaks.[3,18,19]

Currently, four classes of antifungals are used in the treatment of systemic fungal infections (table I). The polyene macrolides include amphotericin B, nystatin, candicidin, natamycin and mepartricin. Another class comprises the azoles, which are subdivided into two groups: the imidazoles (an older group, made up of miconazole, ketoconazole, clotrimazole and econazole); and the triazoles (a newer

Table I. Classes of antifungals and their mechanisms of action

Class	Representative drugs	Mechanism of action
Polyene macrolides	Amphotericin B Nystatin Candicidin Pimaricin Mepatricin	Binding to sterol component of fungal cell membrane, leading to increased permeability
Azoles	Imidazoles: miconazole ketoconazole clotrimazole econazole Triazoles: fluconazole itraconazole posaconazole ravuconazole tetraconazole voriconazole	Inhibition of sterol 14-α-demethylase Erg11p, impairing ability of the fungal cell to produce ergosterol for the cell membrane
Fluorinated pyrimidines	Flucytosine	Inhibition of both DNA and protein synthesis
Echinocandins	Anidulafungin Caspofungin Micafungin	Interference with (1,3)-β-glucan synthesis, leading to loss of fungal cell wall integrity

Table II. Recovery of amphotericin B from tissues (in adults); tissue concentrations were measured in autopsy specimens from 13 adult cancer patients who received a total dose of amphotericin B 75–1100mg

Organ	% Recovered [mean ± SD (range)]
Liver	27.5 ± 6.4 (17.5–40.3)
Spleen	5.2 ± 4.4 (0.7–15.6)
Lungs	3.2 ± 3.3 (0.4–13)
Kidneys	1.5 ± 1 (0.6–4.1)
Heart	0.4 ± 0.4 (0–1.4)
Brain	0.3 ± 0.2 (0–1.4)
Pancreas	0.2 ± 0.2 (0.1–0.6)

group of compounds, including fluconazole, itraconazole, tetraconazole and voriconazole). The third class is fluorinated pyrimidines such as flucytosine; these agents are usually administered with amphotericin B, as resistance can develop rapidly if they are used as monotherapy. A fourth class, the echinocandins, is currently under investigation for use in neonates.

This paper reviews published data about these drugs, as used in the treatment of systemic candidiasis infections in neonates. Data about the pharmacology, indications and efficacy, and toxicity for each of these drugs in this population are presented, and conclusions are drawn from this where possible.

1. Pharmacology

1.1 Amphotericin B

First introduced in 1956, amphotericin B (yes, there was an amphotericin A) is produced by a strain of *Streptomyces nodosus* discovered by Gold and colleagues[20] on decomposing vegetation in the Orinoco river valley of Venezuela. Amphotericin B is a macrocyclic, polyene, antifungal antimicrobial that binds to the sterol component of the fungal cell membrane, leading to increased cell permeability and, ultimately, to cell death.[21] Although amphotericin B has higher affinity for the ergosterol component of the fungal rather than mammalian cell membrane, it also binds with cholesterol components of the mammalian cell membrane and can, therefore, lead to toxicity in patients. Originally, this toxicity was so high that investigators thought the drug would be impractical, and modifications to the polyene structure were made; yet, over time, amphotericin B has proved the least toxic and most effective agent in this class in many systemic infections.[22]

There is essentially no gastrointestinal absorption of amphotericin B, so the drug is given parenterally, combined with deoxycholate to provide solubility in water. Once in the bloodstream, amphotericin B dissociates from the deoxycholate, where more than 90% of the drug then binds to serum proteins, especially β-lipoprotein.[21] Amphotericin B then distributes widely into tissues, especially the liver and spleen (table II). The observed tissue-penetration characteristics correspond well with the prolonged terminal elimination half-life of about 15 days seen in adults (table III).[23,24] There are no such data for neonates. Despite decades of study and clinical use, the exact disposition profile of amphotericin B in humans remains unknown. The drug is known to effectively bind to tissues, which accounts for a prolonged terminal elimination half-life of ~15 days in adults.[21] The drug, regardless of formulation, penetrates poorly into the cerebrospinal fluid (CSF) and central nervous system, even in the presence of meningeal inflammation.[22] Amphotericin B body clearance is unaffected by renal or hepatic disease, although lowering the dose or increasing the dose administration interval may decrease the risk of nephrotoxicity.

Potential pharmacogenetic differences in the metabolism of both amphotericin B and the deoxycholate with which it is administered have been suggested. These drugs, alone or in combination, have the ability to decrease the metabolism of propafenone (a sodium-channel antagonist now used primarily as a probe for metabolic activity) to

Table III. Pharmacokinetic parameters of amphotericin B in neonates

	Starke et al.[25]	Baley et al.[26]
Number in study	4	13
Age	<3mo	Neonates (11 VLBW)
Vd (L/kg)	2.8	1.5
CL (mL/min/kg)	2.5	1.1[a]
CL (mL/min/1.73m^2)	29[a]	18
Serum half-life (h)	27.2	14.8

a Calculated value.

CL = clearance; **Vd** = volume of distribution; **VLBW** = very low birth weight.

5-hydroxy-propafenone (via cytochrome P450 [CYP] 2D6) and then to *N*-desalkyl-propafenone (via CYP1A2 and CYP3A4).[27] Thus, it has been inferred that these CYP isoenzymes may be involved in the metabolism of amphotericin B and deoxycholate. Genetic differences in these enzymes may therefore account for some of the variability seen in the metabolism of amphotericin B deoxycholate.[28] However, there are no data from direct assessment of this issue.

Only two pharmacokinetic studies of amphotericin B in neonates are available (table III). Starke et al.[25] showed that the disposition of amphotericin B was more variable in neonates, and that serum half-life was longer in four of five neonates, than older children. Neither serum concentrations nor pharmacokinetic parameters predicted efficacy or toxicity in this small study. The other pharmacokinetic study, by Baley et al.,[26] showed large inter-individual variation in elimination after 5 days of therapy, and the median serum half-life of amphotericin B was twice that described in previous adult trials.[22]

Taken together, the above data indicate tremendous variability in individual responses to amphotericin B. Such variability may be due to heterogeneity of the patient populations studied so far, in terms of maturity, degree of illness, comorbid conditions and overall management differences that influence mortality.

1.2 Amphotericin B Lipid Formulations

Lipid formulations of amphotericin B were developed in an attempt to decrease the clinical toxicity that occurs with systemically administered amphotericin B deoxycholate. Three formulations are currently available. One is liposomal amphotericin B, which is a unilamellar bilayer liposomal preparation with the amphotericin B component intercalated in the membrane. The liposomes are spheres less than 100nm in diameter that allow drug penetration through the cell wall of susceptible intracellular and extracellular pathogens.[29,30] The second preparation is amphotericin B lipid complex (ABLC), where the drug is complexed in a 1 : 1 ratio with two lipids and looks more like a long ribbon.[7,13,31] The third preparation, amphotericin B colloidal dispersion (ABCD), complexes cholesteryl sulfate in a 1 : 1 ratio with amphotericin B in a disc-like morphology.

The composition of the lipid matrix of an individual formulation influences the product's disposition profile and partially explains the different disposition characteristics between the three lipid-based formulations and conventional amphotericin B deoxycholate.[32] The larger liposome vesicles used in ABLC and the shape of ABCD result in greater uptake by the reticuloendothelial system and increased clearance from the systemic circulation than with liposomal amphotericin B.[33] Further, the electrical charge of the matrix surfaces also influences disposition, with positively charged and neutral liposomes remaining in the circulation longer than smaller, negatively charged moieties.[34] Lastly, the composition of each lipid formulation regulates the release of active, free amphotericin. This may, in part, explain the disparity observed in the incidence of formulation-associated adverse effects.[35]

The above characteristics most likely modulate the pharmacokinetic properties of these three formulations. One possible explanation for the decreased renal toxicity seen with these preparations relative to amphotericin B deoxycholate is that drug release from the lipid matrix is facilitated by lipases produced by inflammatory cells in infected areas, thus targeting areas where more drug is needed and sparing others.[36] Comparative data in adults for the deoxycholate, liposomal and lipid-complex preparations of amphotericin B are summarised in table IV.[29,31,33,37] Differences in tissue distribution are responsible for the variation seen. In the liposomal amphotericin B preparation, the amphotericin B component remains complexed to the liposome for longer periods than in the other preparations, resulting in a higher peak serum concentration (C_{max}) and lower clearance. Similarly, the extensive tissue dis-

Table IV. Comparative kinetics (mean ± SD) of amphotericin B formulations in adults[29,31,33,37]

	Deoxycholate	Liposomal	Lipid complex
Dose (mg/kg)	0.6	5	5
C_{max} (mg/L)	1.1 ± 0.2	83 ± 35.2	1.7 ± 0.8
Vd (L/kg)	5 ± 2.8	0.11 ± 0.08	131 ± 7.7
CL (mL/min/kg)	0.63 ± 0.25	0.18 ± 0.1	7.3 ± 3.1

CL = clearance; **C_{max}** = peak serum concentration; **Vd** = volume of distribution.

tribution of the lipid complex accounts for its larger volume of distribution and clearance. The terminal half-life values for unbound drug should be the same for all four preparations.[29,31,33,37]

The only study that presented fluid concentrations in neonates receiving liposomal amphotericin B reported randomly drawn, steady-state serum and joint-fluid concentrations of 0.57 and 0.79 μg/mL, respectively, for a dosage of 3.5 mg/kg/day.[14] Data from adults show that higher and more prolonged serum concentrations are obtained with the liposomal than either the deoxycholate or lipid-complex preparation.[29,31,33] Adult data infer good tissue penetration based on treatment success rates; however, tissue penetration of these formulations has not been adequately studied in neonates or children.

1.3 Flucytosine

Flucytosine, also known as 5-fluorocytosine or 5-FC, is a fluorinated pyrimidine and member of the antimetabolite family of drugs. Flucytosine enters the cell with the aid of the permease enzyme and, once inside, is converted first to fluorouracil and then to fluorouridylic acid.[21,38] These forms can either be further phosphorylated and incorporated directly into RNA, disrupting protein synthesis, or be metabolised to fluorodeoxyuridylic acid, a potent inhibitor of thymidylate synthetase, thus disrupting DNA synthesis and nuclear division. The fact that mammalian cells do not convert flucytosine to fluorouracil, but fungal cells do, provides the basis for the compound's selectivity. Resistance to flucytosine is conferred through loss of enzymatic activity, leading to either decreased uptake of the drug or decreased conversion to fluorouridylic acid.[21,38]

Flucytosine is rapidly and almost completely absorbed from the gastrointestinal tract.[21] The drug only minimally binds to plasma proteins (<5%), and exhibits a volume of distribution near one, approximating that of water. It is primarily excreted unchanged in the urine, and the rate of clearance is nearly equal, and closely tied, to that of creatinine, so that dosage adjustments are needed in patients with renal compromise. Flucytosine penetrates well into the CSF, with a percentage transference from the serum of 65–90%. Mean tissue concentrations in adults approximate those in serum.[39,40] Flucytosine can be removed by peritoneal dialysis.

Table V. Pharmacokinetic parameters for flucytosine in neonates

	Hill et al.[40]	Baley et al.[26]
Number in study	1	13
Dosage (mg/kg/day)	100	50–100
C_{max} (mg/L)	40	11–44
Vd_{ss} (L/kg)		1.1
Terminal elimination half-life (h)		7.4

C_{max} = peak serum concentration; **Vd_{ss}** = volume of distribution at steady state.

Pharmacokinetic data for flucytosine are shown in table V. After a single oral dose of 25 mg/kg (corresponding to a 100 mg/kg/day dosage divided into four doses), Hill et al.[40] reported serum concentrations at 2, 4 and 6 hours, and CSF concentrations at 6 hours, all well above the initial minimum inhibitory concentration (MIC) for *C. albicans* of 0.1 μg/mL. After 12 days' therapy, this MIC had increased to 62.5 μg/mL, illustrating the rapid resistance that can emerge to flucytosine when used as monotherapy. Baley and colleagues[26] described the multidose pharmacokinetics of flucytosine in 13 infants who received oral flucytosine plus intravenous amphotericin B. The disposition characteristics for flucytosine were highly variable and similar to those seen in adults. However, as flucytosine exhibits time-dependent pharmacodynamic activity, the above data suggest that once-daily administration is adequate for premature and full-term infants with immature renal function.[26]

1.4 Fluconazole

Fluconazole is a triazole member of the azole family. Members of this family, imidazoles and triazoles alike, exert their effects on fungi by inhibiting sterol 14-α-demethylase Erg11p, impairing the ability of fungal cells to produce ergosterol for their membranes.[22] This leads to accumulation of 14-α-methylsterols, which in turn disrupts the packing of phospholipids and interferes with certain membrane-bound ATPases and enzymes of the electron transport chain.[21] Resistance to azole antifungals has occurred during prolonged therapy, often in patients with AIDS. Mutations encoding the gene for 14-α-demethylase confer resistance to all azoles and have been seen in *C. albicans*.[41] Increased azole efflux, secondary to the ATP-binding cassette proteins complementarity-determining region

Table VI. Pharmacokinetic parameters for fluconazole in neonates

Parameter	Wyble et al.[48]	Wiest et al.[53]	Krzeska et al.[54]	Saxén et al.[55]	Marr et al.[47]	Wong et al.[49]	Wenzl et al.[56]
Number in study	3	1	14	12	1	17	3
C_{max} (mg/L)		10.3		10		6.23[a]	
C_{min} (mg/L)		6.98		2.9[b]	9.3[c]	4.15[a]	
Trough CSF (mg/L)					8.1[c]		
Vd (L/kg)		1.24	1.17	2.25		1.23	1.5
CL (mL/kg/min)	0.26	0.67	0.63	0.52		0.27	
Half-life (h)		37.4	22.5	55.2		30.9[a]	36

a Data from non-peritoneal dialysis group.

b Dose given every 72h.

c Dosage 4 mg/kg/day.

CL = clearance; **C_{max}** = peak serum concentration; **C_{min}** = trough serum concentration; **CSF** = cerebrospinal fluid; **h** = hours; **Vd** = volume of distribution.

(CDR) 1 and CDR2, is responsible for resistance to itraconazole and fluconazole.[42] Resistance specific to fluconazole results from increased azole efflux via the major facilitator superfamily transporter multidrug resistance gene 1 in *C. albicans* and *C. glabrata*.[21,42] The various *Candida* species have characteristic MICs to fluconazole therapy. *C. krusei* and *C. lipolytica* appear to have innate resistance and have the highest MICs.[43-45] *C. glabrata* has a slightly lower MIC, followed by *C. lusitaniae* and *C. parapsilosis*.[45] *C. albicans* has the lowest MIC.[44] *C. tropicalis* appears to have a bimodal MIC distribution, one low value (similar to *C. parapsilosis*) and the other quite high (similar to *C. lipolytica*); thus, it is difficult to rank.[45] Time-dependent fungistatic activity best describes the pharmacodynamic properties of fluconazole against sensitive *Candida* species.[46]

The pharmacokinetics of fluconazole are unlike those of amphotericin B in almost every way. Fluconazole is nearly completely absorbed from the gastrointestinal tract, with absorption unaffected by changes in gastric pH or by food.[21,22] The drug may be given parenterally, binds minimally to plasma proteins (12%), and rapidly passes into all body fluids, including the CSF, where concentrations were 50–90% of those observed in the serum of the four neonates studied to date. The role of meningeal irritation in transference of this drug into the CSF remains to be determined.[21,47,48] As renal excretion accounts for 90% of fluconazole elimination, renal dysfunction must be accounted for when determining fluconazole dosage. Fluconazole is dialysable.[22]

There are more pharmacokinetic data in neonates, from case reports and descriptions of case series, for fluconazole (table VI) than amphotericin B. Overall, pharmacokinetic parameters for fluconazole show less variability than those for amphotericin B. However, as for amphotericin B, an element of variability is introduced by differences in patient populations, gestational ages, comorbid conditions and treatment practices, which vary from centre to centre. Fluconazole terminal elimination half-life was noted by Wong et al.[49] to change with age, and this could be a factor to consider when administering this drug.[47] Fluconazole is a specific inhibitor of both CYP2C9 and, to a lesser extent, CYP3A4.[50-52] Such inhibitory activity may account for some of the interindividual variability seen in the above studies. Further studies are needed to assess the significance of genetics to the dosage and administration of fluconazole.

1.5 Echinocandins

The echinocandins represent the first group of novel drugs clinically available for the treatment of systemic fungal infections in more than two decades.[57] Echinocandins are semisynthetic derivatives of echinocandin B, first isolated from *Aspergillus nidulans* in 1974.[58] Although structure-activity relationships for these agents are still under investigation, it appears that both the central ring and side chain are necessary for antifungal activity, with alterations in composition of the side chain and

other attached moieties influencing *in vitro* activity.[59] These agents distinguish themselves from other available antifungal drugs in their ability to rapidly and noncompetitively interfere with the synthesis of fungal cell (1,3)-β-glucan, a glucose polymer essential for the structural integrity of most fungal cell outer membranes. Interference with (1,3)-β-glucan synthesis leads to the development of an incompetent cell wall and ultimately to cell lysis.[57,59] This cellular mechanism of action is unique among currently available antifungal drugs and thus circumvents pathogen cross-resistance. The exact mechanism of how echinocandins interfere with (1,3)-β-glucan synthesis is unclear but appears to be the drugs' ability to interfere with expression of the gene product controlling glucan synthesis.[57] Current data suggest that the pharmacodynamic properties of echinocandins are best characterised by concentration-dependent activity.[32]

The spectrum of antifungal activity of the echinocandins continues to be elucidated. Unfortunately, some controversy exists regarding their overall *in vitro* and *in vivo* antifungal activity because of disparities that may be due to variability in the methods of *in vitro* analysis.[57] To date, these drugs have repeatedly demonstrated potent *in vitro* activity against *Candida* spp., *Aspergillus* spp., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Pneumocystis carinii* and *Coccidioides immitis*.[57,59] Fungi with limited to no (1,3)-β-glucan within their cell walls are resistant to the echinocandins, and include *Cryptococcus neoformans* and members of the order Mucorales. The relevance of *in vitro* susceptibility data to therapeutic outcome for the echinocandins remains to be better defined. For example, *in vitro* testing suggested resistance of *A. fumigatus* to one echinocandin analogue, whereas echinocandins markedly prolonged the survival of mice and rabbits infected with *A. fumigatus* but without any substantive change in tissue fungal colony counts.[57,60]

Caspofungin, a pneumocandin, is the first echinocandin analogue available for clinical use in the US. It appears that micafungin (FK-463) will be the next agent clinically available. Unfortunately, very limited pharmacokinetic data about use of these agents in humans, and none about use in infants, have been published. From adult studies, caspofungin appears to have very poor oral bioavailability, requiring parenteral administration. The drug is ~96% protein bound and extensively metabolised, with a terminal elimination half-life in adults of 9–10 hours. Approximately 3% of an administered dose is recovered unchanged in the urine. The route or routes of metabolism, exact metabolites, and antifungal activity, if any, of these metabolites remain to be determined. A recent abstract describes only modest increases in caspofungin plasma concentrations in adults with mild to moderate hepatic insufficiency.[61] The investigators suggest that dosage adjustment is not required in patients with mild hepatic insufficiency, whereas dosage reduction is probably needed in patients with moderate insufficiency.[61]

Caspofungin pharmacokinetic data determined in two post-liver transplant patients aged 9 months and 5 years, and who were receiving 1 mg/kg intravenously once daily, revealed the following respective values: C_{max} 4.0 and 8.8 mg/L; terminal elimination half-life 11.7 and 10.7 hours; volume of distribution 0.24 and 0.11 L/kg; and clearance 0.24 and 0.12 mL/min/kg.[62] The data observed in this infant and child appear similar to published data for adults; however, the tremendous variability observed underscores the need to determine the disposition characteristics of echinocandins over a broad age range.[59]

Similar to caspofungin, micafungin is also poorly bioavailable, necessitating intravenous administration. The drug is extensively metabolised via hepatic and extrahepatic pathways and exhibits a terminal elimination half-life of ~13 hours. To date, six micafungin metabolites have been identified, although their route or routes of metabolism and antifungal activity, if any, are not known.[63] Mukai et al.[63] recently described in abstract the comparative disposition characteristics of FK-463 in elderly (aged 66–78 years) versus non-elderly (aged 20–24 years) healthy, male volunteers. No differences in micafungin disposition characteristics were observed between the two age groups: C_{max} ~4.9 mg/L, terminal elimination half-life ~15 hours, steady-state volume of distribution ~0.23 L/kg, and body clearance ~11 mL/h/kg. The drug was 99% bound to plasma proteins. Recognising the dependence of hepatic functional maturity on gestational and postconceptional age, these data suggest that echinocandin dos-

ages may need to be modified in premature and newborn infants as compared with adults.

2. Efficacy

2.1 Amphotericin B (With and Without Flucytosine Co-Treatment)

Many studies of the efficacy of amphotericin B have been conducted over the past three decades; however, most of these are retrospective reports. All but one of these, a small, comparative study of amphotericin B with fluconazole,[64] have been given an evidence rating of III by the US Pharmacopeia, meaning "Evidence from clinical trials with low power, preliminary reports of trials in progress, opinions of respected authorities on the basis of clinical experience, descriptive studies such as case reports or series, or reports of expert committees". As amphotericin B and flucytosine are frequently used together, there is no way to determine whether the salubrious effect of therapy is attributable to one or the other drug independently or to a combination of both. Thus, clinical trial data for both compounds are generally presented together. They are summarised in table VII.

In 1978, Chesney et al.[76] published their report of a 28-week gestational age neonate with candidal meningitis. The paper also contained a review of the 17 cases of candidal meningitis in neonates, 15 of whom were premature, reported to that point.[40,77-87] Four of these 17 infants were not treated and, of these four, half died and half sustained neurological damage. Of the 13 treated infants, three (23%) died and, of the 10 survivors, seven (70%) developed aqueductal stenosis or neurodevelopmental delay. The other three survivors were developmentally appropriate.

In 1984, Faix[65] reported a case series of 27 infants, 19 of whom were very low birth weight (VLBW), with systemic candidiasis. This researcher suggested that amphotericin B alone may have been insufficient for treating CNS infection and suggested, but did not demonstrate, that added flucytosine may have been needed for a successful outcome. The study by Smego and Perfect[66] did not prove the superiority of combined amphotericin B and flucytosine in treating candidial meningitis, but did suggest that intravenous amphotericin B might be more important than intrathecal drug in treating such infection.

Evdoridou et al.[14] reviewed available data about osteoarticular infections due to *Candida* spp. in neonates and found that, of the eight reported cases treated with amphotericin B, there was one death (12.5%). The other patients recovered or improved with therapy.[14,81,87-92]

There are two reports of successful treatment of candidial endocarditis without surgical intervention.[74,75] Each describes three neonates successfully treated with amphotericin B (five of whom also received flucytosine) and who had gradual improvement in their clinical condition and echocardiographic findings. In the one child who died (from an unrelated cause) there was no evidence of endocarditis at autopsy.

Because of the many confounding variables and heterogeneity of the study populations described, it is difficult to derive meaningful data from these studies. Nevertheless, these experiential data do suggest the clinical efficacy of amphotericin B combined with flucytosine for the treatment of systemic candidiasis. Several investigators reported pathogen MICs or minimum fungicidal concentrations (MFCs) for amphotericin B, and these were fairly consistent throughout the different populations.[25,26] Baley et al.[26] also observed that patients tended to survive when the serum amphotericin B concentration was at least 1.5 times the MIC. However, one cannot make meaningful predictions about the dosage of amphotericin B and its relationship to MIC during treatment, as the drug tends to accumulate in tissues (in adults and probably in neonates as well) at differing rates.

In vitro MIC limits for amphotericin B therapy have been determined for various *Candida* isolates and are presented in table VIII.[93] There is only one report that correlates clinical outcomes of candidiasis with *in vitro* MIC values in neonates.[94] The investigators analysed 38 isolates according to the microdilution method approved by the National Committee for Clinical Laboratory Standards in its document M-27-A.[95] A firm definition of susceptibility and resistance as related to MIC was not given in this paper for amphotericin B (although it was for fluconazole and flucytosine); nonetheless, the obser-

Table VII. Efficacy of amphotericin B (with and without flucytosine co-treatment)

Study	Number in study	Location of infection	Dosage (mg/kg/day)	Flucytosine dosage (mg/kg/day)	Duration of treatment (days)	Complications	Survival rate [number of patients (%)]	Comments on survival rate
Faix[65]	27 (19 VLBW)	Systemic	0.1 increased to 0.5–1[a]	150 (some)	Varied		18/27 (67)[a]	
Smego & Perfect[66]	17 (7 neonates)	Meningitis	0.5–1[a]	90–200	39–120		14/17 (82)	Eight patients were untreated All deaths were premature neonates Two infants who received only IT amphotericin B died
Johnson et al.[4]	5	Systemic (two with meningitis as well)	0.1	Not stated		Intracardiac catheter infection	5/5 (100)	
Hall et al.[67]	5	Systemic	0.5	None	>30		3/5 (60)	
Loke et al.[68]	22 VLBW	Systemic/ pneumonia	0.1, increased to 0.3–0.5	100			18/22 (82)	
Butler et al.[69]	36	Systemic	0.25, increased to 1	None		Catheter-associated infection	28/36 (78)	All deaths were in the catheter-associated group Only two deaths were considered related to the *Candida* infection
Leibovitz et al.[70]	25	Systemic	0.5–0.6[b]	50–100	13–44		20/25 (80)	Three deaths attributed to candidiasis
Glick et al.[71]	36	Systemic	0.5 or 1[c,d]		25		30/36 (83)	
Donowitz & Hendley[72]	30 children (10 premature)	Systemic	0.5		7–14 after last positive culture		18/30 (60)	Only four of ten premature infants were successfully treated in this manner
Driessen et al.[64]	12	Systemic	1	None	7–31		6/11 (54)	
Fernandez et al.[73]	23	Meningitis	0.25, increased to 1	75–100[e]			14/23 (65)	Only three deaths were attributed to *Candida* infection
Zenker et al.[74]	3	Endocarditis	1	100	42–74		2/3 (67)	Death not attributed to *Candida* infection
Sanchez et al.[75]	3	Endocarditis	0.75–1	150	47–75		3/3 (100)	

a Some received IT therapy as well.

b One patient received 1 mg/kg/day.

c Dosage stratified by weight: under 1kg received 0.5 mg/kg/day; over 1kg received 1 mg/kg/day.

d After cultures were negative, the dosage was administered every other day.

e Received by five subjects.

IT = intrathecal; **VLBW** = very low birth weight.

Table VIII. Recommended minimum inhibitory concentration (MIC) limits for antifungal agents[93]

Organism	Antifungal agent	MIC range (mg/L)	MICs within range (%)
Candida parapsilosis (ATCC 22019)	Amphotericin B	0.25–1.0	99.1
	Fluconazole	2.0–8.0	99.1
	Flucytosine	0.12–0.5	98.6
C. parapsilosis (ATCC 90018)	Amphotericin B	0.5–2.0	96.4
	Fluconazole	0.25–1.0	98.2
	Flucytosine	0.12–0.25	99.5
C. albicans (ATCC 90028)	Amphotericin B	0.5–2.0	91.9
	Fluconazole	0.25–1.0	97.3
	Flucytosine	0.5–2.0	95.0
C. albicans (ATCC 24433)	Amphotericin B	0.25–1.0	99.5
	Fluconazole	0.25–1.0	95.9
	Flucytosine	1.0–4.0	91.9
C. krusei (ATCC 6258)	Amphotericin B	0.5–2.0	99.5
	Fluconazole	16–64	99.1
	Flucytosine	4.0–16	96.8
C. tropicalis (ATCC 750)	Amphotericin B	0.5–2.0	93.7
	Fluconazole	1.0–4.0	95.5
	Flucytosine	≤0.12–0.25	99.5

vation was made that resistance to amphotericin B was likely to be associated with an MIC >1 μg/mL. Huang et al.[94] had a relatively small population (n = 32) from which to draw their conclusions, but suggested that an MIC ≤0.5 μg/mL might be associated with successful amphotericin B or fluconazole therapy (table IX), adding that a larger study needed to be done to lend credence to this estimation. Also, there was no correlation made between MIC for the isolate and serum drug concentration.

In the absence of MIC or MFC data for specific pathogens, no conclusions regarding optimal antifungal drug dosages can be derived. Even the question of whether to add flucytosine to amphotericin B remains a matter of debate in the absence of clear guidelines for flucytosine use.[8] Considering the mortality associated with fungal infections in neonates, the above data would support the use of clinically acceptable, aggressive drug dosages, titrated in line with specific patient tolerance, until more definitive amphotericin B or flucytosine dosages are defined in this patient population. No optimal duration of therapy has been established. Current recommendations for amphotericin B dose administration are to begin with 0.25 mg/kg/day, followed by daily dosage increases of 0.25 mg/kg/day until a therapeutic dosage (usually ≥0.7 mg/kg/day) is reached.[96] In neonates with severe infections, dose increases every 12 hours have been well tolerated.[96] If the infecting isolate is identified as *C. krusei*, a dosage of 1 mg/kg/day is recommended.[97]

2.2 Amphotericin B Lipid Formulations

The high toxicity of amphotericin B prompted investigations into the use of lipid-based preparations as a means of avoiding toxicity but being able to safely deliver a higher dose. Similar to the published data for amphotericin B deoxycholate, most experience with amphotericin B lipid formulations in neonates is derived from individual case studies. The studies presented here used liposomal amphotericin B, with the exception of the study by Adler-Shohet et al.[98] that used ABLC, and the study of López Sastre et al.,[99] which used both liposomal and ABLC preparations, are summarised in table X. There are no studies comparing efficacy of the liposomal with deoxycholate preparations in neonates.

López Sastre et al.[99] recently published their prospective study of 118 neonates with invasive candidiasis. Maximal daily doses used in this report were similar to those used by other investigators. They noted that the efficacy of treatment with liposomal amphotericin B (94%) was similar to that with the lipid complex (86%). All deaths in this study occurred in the VLBW group.

Considerable variability, in terms of patient population, medical management and study methology, exists in the above studies; thus, the optimal dosage of amphotericin B lipid formulations has not been defined, nor has the optimal duration of therapy. As

Table IX. Correlation of minimum inhibitory concentration (MIC) with successful treatment[94]

Drug	MIC (mg/L)	Number of patients	Success [number (%) of patients]
Amphotericin B	0.25	3	3 (100)
	0.5	4	3 (75)
	1	22	12 (55)
	2	3	2 (67)
Fluconazole	0.25	1	1 (100)
	0.5	3	2 (67)
	1	5	2 (40)
	4	2	2 (100)
	8	3	2 (67)
	16	1	1 (100)

Table X. Efficacy of amphotericin B lipid formulations in neonatal fungal infections

Study	No. pts	Location of infection	Formulation	Dosage (mg/kg/day)	Duration of treatment (days)	Survival rate [number (%) of patients]	Comments
da Silva et al.[100]	2	Systemic	Liposomal	1, increased to 1.25	14	≥1/2 (≥50)	One child survived, no data on the other
al Arishi et al.[101,102]	2	Blood + urine/ blood + CSF	Liposomal	2, increased to 3 or 5		2/2 (100)	Patients were also treated with flucytosine
Scarcella et al.[103]	44	Systemic/joint/ meningitis	Liposomal	1, increased to 5	7–49 (mean 22)	32/44 (72)	All who died were very low birth weight
Weitkamp et al.[5]	21	Systemic	Liposomal	1, increased up to 5	11–79 (mean 28)	21/21 (100)	
Juster-Reicher et al.[104]	24	Systemic	Liposomal	1, increased to 6	2–31 (mean 21)	23/25 (92)	
Adler-Shohet et al.[98]	11	Systemic	ABLC	3.2–6.5 (mean 4.9)	4–41 (median 23)	9/11 (81)	Prior therapy: AMB (with or without nephrotoxicity One patient died with negative cultures
López Sastre et al.[99]	110	Systemic	Liposomal (81); ABLC (29)	2.1 ± 1.7, increased to 3.8 ± 1.1 (liposomal); 2.6 ± 1.5, increased to 2.1 ± 1.0 (ABLC);	19 ± 8 (liposomal); 15 ± 6 (ABLC)	76/81 (94%; liposomal); 25/29 (86%; ABLC)	

ABLC = amphotericin B (AMB) lipid complex; **CSF** = cerebrospinal fluid.

for the deoxycholate preparation, the current recommendation for liposomal amphotericin B is to start with a relatively low dosage (in this case 1 mg/kg/day) and increase gradually to a target dosage (usually 5 mg/kg/day). The case reports and few small series outlined above support the efficacy of liposomal and lipid-complex formulations of amphotericin B in premature and newborn infants. Compared with amphotericin B deoxycholate, monotherapy with the liposomal preparation appears to be more effective in treating CSF infections, with six of seven reported children having meningitis successfully treated.[101-103] However, the case-report nature of these data introduces considerable bias towards reporting successful therapy, and the assumption of superior efficacy for the liposomal formulation has not been proved in a comparative study. It is also not clear whether any differences in response are secondary to differences in drug tissue distribution, or to the greater dose of amphotericin B, which is usually five times higher with the liposomal than deoxycholate formulation of amphotericin B (5 vs 1 mg/kg/day).

The above findings are also not surprising, since the lipid matrices are simply carrier molecules for amphotericin B with differences only in rates of drug release.[105] The slower release rates of active amphotericin B from lipid preparations rather than the conventional deoxycholate formulation are reflected in increased patient tolerance and safety with dosages greater than those possible with the deoxycholate formulation.[106] However, differences in clinical efficacy relative to drug-release characteristics may be important and require close scrutiny.

2.3 Flucytosine

There is a paucity of data addressing the clinical efficacy of flucytosine monotherapy, as it soon became apparent that pathogen tolerance rapidly developed to this drug when used alone.[40,107,108] We were able to identify only three infants (and no neonates) in the literature with systemic candidiasis treated with flucytosine monotherapy; all were treated successfully with a daily dose of 100–200 mg/kg (table XI).[109] Five other infants with candidial urinary tract infection were treated successfully with a much lower dosage (25–50 mg/kg/day), possibly

Table XI. Efficacy of flucytosine in neonatal fungal infections

Parameter	Isacson et al.[109]	Smith & Congdon[111]	Holt & Newman[110]
Number in study	3	10	5
Location of infection	Systemic	Systemic	Urinary tract
Dosage (mg/kg/day)	100–200	100–215	50, reduced to 25
Duration of treatment (days)	60–90	9–33	16–77 (mean 39)
Survival rate [number (%) of patients]	3/3 (100)	6/10 (6)[a]	4/5 (80)[b]

a Deaths were not attributed to candidiasis.

b One child had recrudescence of infection; minimum fungicidal concentration had increased.

because of the ability of flucytosine to concentrate in the urine.[110]

2.4 Fluconazole

The vast majority of published data for antifungal drug use in neonates involves fluconazole. As for amphotericin B, most of the published experience is derived from uncontrolled retrospective or prospective series, with the paper by Driessen et al.[64] serving as the lone exception (table XII). Overall, these noncomparative trials are insufficient to describe the optimal dosage or duration of therapy for fluconazole. The currently recommended fluconazole dosage is 5–6 mg/kg/day given orally or intravenously.[96] As noted with amphotericin B, fungal MICs greater than the actual serum concentrations attained were associated with mortality. However, the type of resistance seen in, among others, fluconazole-treated AIDS patients was not reported. As for the ability of MICs to predict successful treatment, Huang et al.[94] observed 15 neonates receiving fluconazole therapy, as discussed in section 2.1. The correlation of fluconazole MIC with clinical success was nonexistent in their study, and, as for amphotericin B, there were no documented serum drug concentrations to correlate with the clinical data.[94]

As for amphotericin B, case reports by Oleinik et al.[89] and Marr et al.[47] supported the possible synergistic use of fluconazole with flucytosine. Unfortunately, there was only one patient described in each of these reports, making this a rather weak reed upon which to lean for support, and further studies are necessary here as well.

The role of fluconazole as a prophylactic agent has recently been described.[119] In this study, 50 preterm infants were treated with fluconazole 3 mg/kg every third day for 2 weeks, every other day for the third and fourth weeks, and daily for the fifth and sixth weeks. No invasive fungal infections were observed in this group, compared with ten cases (20%) in 50 matched controls.

3. Toxicity

3.1 Amphotericin B

Amphotericin B is the most commonly used antifungal drug for the treatment of disseminated fungal infections in neonates, but some babies develop adverse effects necessitating treatment withdrawal. The drug is primarily nephrotoxic, induces systemic electrolyte abnormalities and, to a lesser extent, is cardiotoxic.[21,22] The nephrotoxicity is cumulative and is characterised by antidiuretic hormone-resistant polyuria, renal tubular acidosis, hypokalaemia and renal failure. These effects are thought to be the result of amphotericin B-induced vasoconstriction, resulting from increased intracellular calcium in arteriolar smooth muscle, and from increased permeability of the cell membrane caused by amphotericin B binding to cholesterol in the membrane.[120,121] Cardiodepression appears to be due to decreased activation of slow calcium channels and inhibition of sodium efflux.[122]

Several authors have reported the toxicity of amphotericin B in neonates, as summarised in table XIII**.** Most authors who evaluated the tolerability of amphotericin B in neonates noted changes in renal function (as evidenced by changes in serum blood urea nitrogen, creatinine and/or electrolytes), and frequently this was reversible. It is not clear whether these changes are the result of therapy or of the disease itself. As shown by Butler et al.[69] and Fernandez et al.,[73] altered renal function attributed to amphotericin B toxicity was seen in some infants

Table XII. Efficacy of fluconazole in neonatal fungal infections

Study	Number in study	Location of infection	Dosage (mg/kg/day)	Duration of treatment (days)	Survival rate [number (%) of patients]	Comments
Driessen et al.[64]	12	Systemic	10 on first day, decreased to 5	3–39 (mean 21)	8/12 (67)	
Wyble et al.[48]	3	Systemic	3–6	Not specified	3/3 (100)	Prior therapy: AMB ± 5-FC
Fasano et al.[112]	32	Systemic	1–16 (mean 5.3)	2–80 (mean 26)	31/32 (97)	
Bilgen et al.[113]	10	Systemic	6	Not specified	9/10 (90)	One patient had a high MIC for fluconazole, and was switched to AMB Therapy was intravenous followed by oral therapy
Narang et al.[114]	23	Systemic	5	21–28	19/23 (83)	
Merchant et al.[115]	8	Arthritis	7	42	≥6/8 (75)	Only six patients had culture-proven arthritis Therapy was intravenous and oral One patient died, and one was lost to follow-up
Wainer et al.[116]	20	Systemic	5	3–57 (mean 25)	13/19 (68)	One patient died, and one was lost to follow-up Five of the deaths were not related to fungal infection
Driessen et al.[117]	21	Systemic	5	1–42 (mean 27)	19/21 (91)	Oral dose used
Huttova et al.[118]	40	Systemic	6	6–48	32/40 (80)	AMB co-treatment was required by six patients

5-FC = flucytosine; **AMB** = amphotericin B; **MIC** = minimum inhibitory concentration.

before initiation of therapy, and some renal-function parameters actually improved with continued treatment. There is no evidence to support the use of serum-concentration or cumulative-dose monitoring as a means of predicting or assessing toxicity.[123]

The data outlined above, though variable and incomplete, reflect an adverse effect profile for amphotericin B in neonates similar to that observed in children and adults. Although the numbers of reported patients are small, with no stratification for gestational/postconceptional age, disease severity, or inherent major organ capacity, these data nevertheless suggest that, like other patient populations, premature and full-term infants tolerate intravenous amphotericin B therapy when the dosage is individually titrated according to patient response.

3.2 Amphotericin B Lipid Formulations

The lipid preparations of amphotericin B owe their existence to the frequent occurrence of toxicity associated with the conventional deoxycholate formulation and have been suggested as a safer alternative. Many investigators have reported generally good tolerability for these preparations, as seen in table XIV. The reports of Adler-Shohet et al.[98] and López Sastre et al.[99] both systematically reviewed the toxicity of ABLC; all other studies used the liposomal preparation. Nevertheless, the incidence of drug/formulation-associated toxicities reported thus far does not appear to reflect any major differences between the lipid and deoxycholate formulations of amphotericin B.

The overall percentage of babies reported in table XIV and who tolerated liposomal amphotericin B was 72% (68 of 94), compared with 78% of those treated with amphotericin B deoxycholate (117 of 150). Rates of renal toxicity were identical between liposomal amphotericin B and the deoxycholate preparation: 22% (33 of 147) and 22% (23 of 106), respectively. Liposomal amphotericin B was also associated with liver toxicity in four patients. It is important to keep in mind that the toxicities of different dosages are being compared. The populations being compared also differ: 15 of the 94 babies (16%) treated with a lipid preparation had previously been treated with the deoxycholate formulation before being switched for reasons of toxicity and/or treatment failure. Patients given the liposomal rather

Table XIII. Toxicity of amphotericin B in studies in neonates

Study	Number in study	Location of infection	Dosage (mg/kg/day)	Flucytosine dosage (mg/kg/day)	Duration of treatment (days)	Number of patients with				Adverse event rate [number (%) of patients]
						hypokalaemia	elevated BUN/Cr	decreased urine output	hepatotoxicity	
Baley et al.[124]	10	Systemic	0.1, increased to 1	Varied		7	7		5	7/10 (70)[a]
Turner et al.[125]	13	Systemic	0.4–1	10–54		6 (transient)	6 (transient)			6/11 (54)
Baley et al.[26]	13	Systemic	Varied (mean 0.54)	Varied (mean 55.4)		5				5/13 (38)
Butler et al.[69]	36	Systemic	0.25, increased to 1				4 (transient)[b]			4/36 (11)
Glick et al.[71]	36	Systemic	0.5–1							0/36 (0)
Kingo et al.[126]	18	Systemic				2		2		4/18 (22)
Fernandez et al.[73]	23	Meningitis	0.25, increased to 1		9–52 (median 31)		7[c]			7/23 (35)

a Six patients died.

b Eight patients had similar elevations before therapy.

c Three patients had abnormal values before therapy, others normalised after a dosage change.

BUN = blood urea nitrogen; **Cr** = creatinine.

than deoxycholate preparation received, on average, a 5-fold greater dosage of amphotericin B, and it has not been shown how the toxicities would compare at similar dosages. Several authors reported that patients tolerated amphotericin B better after switching from the deoxycholate to liposomal preparation.

3.3 Flucytosine

Most of the toxicity data described for systemic flucytosine therapy have been derived from experiences with adult patients, where the most severe complication is neutropenia and thrombocytopenia resulting from drug-induced myelosuppression.[15] Transient elevations of liver enzymes have also been reported in adult patients; these levels have returned to baseline with discontinuation of therapy. Flucytosine-associated toxicity is more severe in individuals with persistent serum flucytosine concentrations >100 μg/mL, supporting the value of serum flucytosine concentration monitoring in patients with compromised renal function. Without drug concentration-monitoring capabilities, flucytosine dosage should be based on glomerular filtration rate. Since mammalian cells appear incapable of deaminating flucytosine to fluorouracil, systemic toxicity is probably due to conversion of flucytosine to fluorouracil by enteric flora.[128]

Unfortunately, insufficient published experience is available to characterise the toxicity profile of flucytosine in infants. Of the data reported and reviewed above, tolerability in neonates appears good, with few flucytosine-induced adverse effects occurring. Interestingly, when serum flucytosine concentrations have been reported in neonates, they have usually been well below the implied toxic-threshold concentration of 100 μg/mL. Holt and Newman[110] reported no haematological or biochemical abnormalities during treatment of five infants given an initial dosage of 50 mg/kg/day, reduced to 25 mg/kg/day (after serum levels were found to be too high), for a mean of 39 (range 16–77) days.[110]

3.4 Fluconazole

All the azole compounds appear to share a similar pattern of associated adverse effects, which are largely gastrointestinal in nature.[21,118] Nausea and vomiting are the most frequent adverse effects asso-

Table XIV. Toxicity of amphotericin B lipid formulations in studies in neonates

Study	Nunber of patients	Dosage (mg/kg/day)	Other treatment	Duration of treatment (days)	Number of patients with			Adverse event rate [number (%) of patients]
					hypokalaemia	elevated BUN/Cr	hepatotoxicity	
Lackner et al.[127]	2	1.5, increased to 5						0/2 (0)
da Silva et al.[100]	2	1.25					1 (transient)	1/2 (50)
al Arishi et al.[101,102]	2	3 and 5	Fluconazole[a]				2 (transient)[b]	2/2 (100)
Scarcella et al.[103]	44	1, increased to 5		7–49 (mean 22)	16			16/44 (36)
Weitkamp et al.[5]	21	1–5 (median 3.8)		11–79 (median 28)	3 (reversible)[c]			3/21 (15)
Juster-Reicher et al.[104]	24	2.5–7 (median 6)		2–31 (median 21)			1	1/24 (4)[d]
Adler-Shohet et al.[98][e]	11	3.2–6.5 (mean 4.9)						0/11 (0)
López Sastre et al.[99]	110 (81 liposomal; 29 ABLC)[f]	2.1 ± 1.7, increased to 3.8 ± 1.1 (liposomal); 2.6 ± 1.5, increased to 2.1 ± 1.0 (ABLC)		19 ± 8 (liposomal); 15 ± 6 (ABLC)	14 (10 liposomal; 4 ABLC)	6 (5 liposomal; 1 ABLC)		≥33/110 (30%) [overall rate not given]

a In one patient.

b Temporally related to parenteral nutrition.

c Seven patients had hypokalaemia before treatment.

d Three infants who developed hypokalaemia on deoxycholate had normalisation of potassium levels when switched to the liposomal formulation.

e Used amphotericin B lipid complex. Others used the liposomal formulation.

f 23/81 (28%) of the lipid complex and 10/29 (34%) of the ABLC groups had thrombocytopenia.

ABLC = amphotericin B (AMB) lipid complex; **BUN** = blood urea nitrogen; **Cr** = creatinine.

Table XV. Toxicity of fluconazole in studies in neonates

Study	No. pts	Dosage (mg/kg/day)	Duration of treatment (days)	Number of patients with elevated transaminase/ GGT	elevated bilirubin	anaemia	elevated BUN/Cr	eosinophilia	Adverse event rate [no. (%) of pts]
Fasano et al.[112]	32	1–16 (mean 5.3)	2–80 (mean 26)	1 (transient)		1 (transient)			2/32 (5)
Merchant et al.[115]	6	7.5	42						0/6 (0)
Wainer et al.[116]	17	5	3–57 (mean 25)	8	4			6	9/17 (53)
Driessen et al.[117]	21	5		7 (transient)					7/21 (33)
Huttova et al.[118]	40	6		2 (transient)			2 (transient)		4/40 (10)

BUN = blood urea nitrogen; **Cr** = creatinine; **GGT** = γ-glutamyl transferase; **pts** = patients.

ciated with azole administration, occurring in up to one-third of patients in a dose-dependent manner. Hepatotoxicity has been reported in 2–10% of patients and ranges from clinically insignificant increases in serum transaminase levels to rare fulminant hepatitis.[21,22]

Available data for fluconazole in neonates are summarised in table XV. Compared with amphotericin B, fluconazole toxicity appears to be much milder and less frequent. In a small series,[115] no abnormalities were reported, whereas in larger series, there was more evidence of toxicity (elevations of hepatic transaminases or γ-glutamyl transferase), although this was mild and usually reversible.[116-118] Wainer et al.[116] also pointed out that the elevated liver-function test results seen in their study could have been caused by an uncontrolled-for high percentage of bacterial and spirochaetal infections.

4. Future Directions

The data collected about the antifungal drugs discussed in this paper represent a tremendous effort on the part of many investigators to define the most efficacious means of using the compounds, usually under the most challenging of clinical conditions. Certainly, the largely retrospective, noncomparative reports that have been highlighted help with this definition to a degree, but, in the final analysis, we do not have sufficient data to define pharmacokinetic profiles, optimal dosages or toxicity for any of these compounds. Further studies are necessary if the process of optimisation already begun is to continue.

Studies should be conducted in the newborn population to determine the pharmacokinetics of these drugs and how such kinetics vary, if at all, with gestational age and development. Such data would provide the foundation upon which a better understanding of optimal dosages and toxicity could be built. Pharmacogenetic studies should be included here as well, especially for amphotericin B and deoxycholate, which seem to demonstrate the greatest interindividual variability. A better understanding of the correlation between fungal MICs and antifungal drug pharmacokinetics (especially with regard to various tissue compartments) will be helpful in predicting resistance and rationally optimising dosages used, which can then be studied in a prospective manner. The toxicity reports to date suffer from much variability among dosage regimens. A better understanding of optimal dosages should provide more homogeneous therapy and allow better studies of toxicity. Further studies could also help determine whether toxicity results solely from treatment, from an intercurrent disease process, or from a combination of both.

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