Published in final edited form as:

Curr Drug Metab. 2013 February 1; 14(2): 193–202.

Triazole use in the nursery: fluconazole, voriconazole, posaconazole, and ravuconazole

Kevin Watt^{1,2}, Paolo Manzoni³, Michael Cohen-Wolkowicz^{1,2}, Stefano Rizzollo³, Elena Boano³, Evelyne Jacqz-Aigrain⁴, and Daniel K. Benjamin Jr.^{1,2}

¹Department of Pediatrics, Duke University, Durham, NC, USA

²Duke Clinical Research Institute, Durham, NC, USA

³Neonatology and NICU, S. Anna Hospital. Torino. Italy

⁴Department of Paediatric Pharmacology and Pharmacogenetics, Clinical Investigation Center Inserm CIC 9202, Hôpital Robert Debré, Paris, France

Abstract

Invasive fungal infections in infants admitted to the neonatal intensive care unit are common and often fatal. The mainstay of therapy against invasive fungal infections is antifungal agents. Over the last two decades, the development and approval of these drugs evolved tremendously, and the azole class emerged as important agents in the treatment and prevention of invasive fungal infections. Among the azoles, fluconazole has been used extensively due to its favorable pharmacokinetics, excellent activity against *Candida* spp, and safety profile. This drug has been well studied in children but data for its use in infants are largely limited to *Candida* prophylaxis studies. Voriconazole, a second generation triazole, has excellent activity against *Candida* and *Aspergillus* spp. However, data on its use in neonates are extremely limited. Posaconazole and Ravuconazole are the newest agents of the triazole family. The antimicrobial spectrum of posaconazole is similar to voriconazole, but with additional activity against zygomycetes. Experience with posaconazole in children is very limited, and there are no reports of its use in infants. Ravuconazole is not approved for use by the FDA but studies in animals and humans show that it is often fungicidal and has favorable pharmacokinetics. In conclusion, the management of invasive fungal infections has progressed greatly over the last two decades with the azole antifungals playing a significant role. Related to this class, future research is needed in order to better assess dosing, safety, schedules and areas of use of these agents in infants admitted to the neonatal intensive care unit.

Keywords

antifungal agents; triazole; prematurity; infection; candida; aspergillosis

BACKGROUND

Invasive fungal infections in infants admitted to the neonatal intensive care unit (NICU) cause significant morbidity and death. Invasive fungal infections account for ~10% of nosocomial sepsis in very low birth weight (VLBW, <1500 g birth weight) infants [1]. The cumulative incidence is ~1–4% for all NICU admission and affects 20% of infants <750 g

Corresponding Author: Daniel K. Benjamin, Jr, MD, PhD, MPH, Professor, Duke University, Pediatrics, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715, Ph: 919 668 8295, danny.benjamin@duke.edu.

Dr Manzoni, MD; Dr Rizzollo, MD; Dr Boano, RN; and prof Jacqz-Aigrain, PhD, have nothing to disclose related to this article.

birth weight [2–8]. Mortality is high (20–30%) even with appropriate therapy [1, 3, 5] and survivors suffer from high rates (59–73%) of long-term neurodevelopmental impairment [3, 9, 10].

The majority of invasive fungal infections in neonates and infants are due to *Candida* spp. Other species (e.g. *Aspergillus* spp. and *Malassezia* spp.) are rare in this population [3, 5, 7]. *C. albicans* accounts for the majority of infections, but *C. parapsilosis* is emerging as a pathogen and accounts for 25% of invasive fungal infections in VLBW infants [11, 12]. Other species such as *C. glabrata* and *C. krusei* which are often resistant to azoles are becoming more important in adult populations [13–18] but have not yet emerged as significant pathogens in the NICU [7, 19–21].

The clinical presentation of fungal infections is difficult to distinguish from other invasive bacterial infections [22]. Further, cultures often take a long time for isolates, if any, to grow [23], and may show poor sensitivity even in the presence of confirmed meningoenitis [3]. Sensitivity is also limited due to the low volume (<1mL) drawn for most neonatal blood cultures. As a result, infants are frequently exposed to empirical antifungal therapy. Given susceptibility patterns, ease of administration, and excellent safety profile, azole antifungal agents are often used as first line therapy for invasive fungal disease and prophylaxis in infants.

TRIAZOLES

The azole antifungals can be divided into two main classes: imidazoles and triazoles. These two classes differ based on the number of nitrogens in the azole ring which results in different binding affinities for the cytochrome P450 enzyme system [24]. The imidazoles, with the exception of ketoconazole, are primarily used for superficial fungal infections. The triazoles are most commonly used for invasive fungal infections and can further be classified in first generation (e.g. fluconazole, itraconazole) and second generation triazoles (e.g. voriconazole, posaconazole, and ravuconazole).

Mechanism of Action

The triazole antifungals inhibit the cytochrome P-450 dependent enzyme lanosterol 14- α -demethylase. This enzyme is necessary for the conversion of lanosterol to ergosterol which is an essential component of the cellular membrane of fungi. Disruption of ergosterol synthesis leads to damage of the cellular membrane by increasing its permeability. The increased permeability of the cellular membrane of fungi results in cell lysis and death [25–27].

FLUCONAZOLE

Fluconazole has excellent activity against *Candida* spp and a low side-effect profile making it a first-line drug for invasive candidiasis (IC) [28–36]. Unfortunately, with widespread use has come emerging resistance and an alteration of the epidemiology of candidiasis in adult populations [29, 37–47]; *Candida glabrata* is now the most commonly isolated *Candida* spp from adult patients with IC [16, 31, 34, 48–51], and some nurseries have reported *Candida glabrata* as a predominant fungal pathogen [52].

Pharmacology

Fluconazole is available in both intravenous (IV) and oral formulations with rapid absorption from gastrointestinal tract and ~92% bioavailability compared with the IV form. It has low protein binding and excellent penetration into the CSF with concentrations ~80% of those found in the serum. Penetration into other body tissues such as joint spaces, saliva,

vaginal secretions, and vitreous humor of the eye also approximate levels found in the serum. Fluconazole is eliminated primarily through the kidneys and excreted largely unchanged resulting in urine concentrations 10–20 times higher than those found in blood [53, 54].

In both *in vitro* and *in vivo* studies, fluconazole has shown activity against *Cryptococcus neoformans* and several *Candida* spp including *C. albicans* and *C. parapsilosis* [55]. *C. krusei* is inherently resistant to fluconazole. *C. glabrata* tends to show intermediate to complete resistance with the minimum inhibitory concentration required to kill 90% of organisms (MIC₉₀) 16 µg/mL. An *in vitro* time-kill study showed that the rate of fluconazole fungistatic activity was not influenced by concentration once the maximal fungistatic concentration was surpassed (concentration-independent), which is in contrast to the concentration-dependent fungicidal activity of amphotericin B deoxycholate or caspofungin [56, 57].

Pharmacokinetics in Children

Scaling of the corresponding adult dosage of fluconazole on a body weight basis is inappropriate for pediatric patients. A review of 5 separate fluconazole pharmacokinetic (PK) studies in 113 children, including 12 premature neonates [58] showed that fluconazole clearance is generally more rapid in children than adults, with a mean plasma half-life of approximately 20 hours compared to approximately 30 hours in adults. Therefore, to achieve comparable exposure in children, the daily fluconazole dose needs to be essentially doubled. Correct pediatric fluconazole dosing should be proportionately higher than adult doses, generally 12 mg/kg/day.

In neonates the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dose for neonatal patients is also necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be due to the larger amount of body water found in the total body volume of neonates [58]. Neonates require approximately 5 days to reach steady-state [59], and maintenance fluconazole doses of 12 mg/kg/day are necessary to achieve exposures similar to older children and adults [60]. Thus, a loading dose of 25 mg/kg to achieve steady state concentrations sooner than the traditional dosing scheme may be appropriate. Preliminary data from a phase 1 trial investigating a fluconazole loading dose in 12 critically ill children showed that the therapeutic target (AUC_{0–24} = 400 ug*h/mL) was reached with the loading dose in 72% of subjects with no related adverse events [61].

Toxicities, Side Effects, and Drug Interactions

Side effects of fluconazole are uncommon. Safety studies have found limited hepatotoxicity compared with the other azoles [55]. In one study of 24 immunocompromised children, elevated transaminases were observed in only two cases [62]. A review of 726 children under the age of one year given fluconazole showed that this drug was generally well-tolerated, and reaffirmed the guidelines to increase the interval between doses due to the prolonged elimination during the first month of life [63]. The safety profile of fluconazole was assessed for 562 children ages 0 to 17 years through the review of 12 clinical trials of fluconazole in children [55, 64]. Most children received multiple doses of fluconazole either orally or via IV injection that ranged from 1 to 12 mg/kg. Many of the patients enrolled in the study had a severe underlying illness and were on a variety of concomitant medications, including chemotherapeutic agents. Fluconazole was overall well tolerated. Fifty-eight children (10.3%) reported transient, treatment-related side effects, most commonly vomiting or diarrhea. Only 3 children (0.5%) had liver-related side effects including elevated liver enzymes, elevated bilirubin, or hepatomegaly. All three of these children had leukemia and

the chemotherapy was also implicated as a possible cause for the hepatotoxicity. This toxicity did not appear to be related to the dosage or total drug exposure. There have been very few studies specifically looking at the safety of fluconazole among neonates. Most of the data comes from the growing body of literature assessing fluconazole prophylaxis in this population. Five randomized controlled trials addressing this question also looked at the effect of fluconazole on liver function tests [52, 65–68]. These five studies included 726 infants in the NICU and two found statistically though not clinically significant increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). All of these values returned to baseline after discontinuation of fluconazole in those infants that survived to discharge.

Neonatal Clinical Studies

Several studies have suggested that triazoles may be a better alternative to amphotericin B deoxycholate because they have a similar broad spectrum of coverage with fewer side effects [29]. An early study of 40 neonates and infants (aged 2 days to 3 months) with either non-response or contraindication to standard antifungal therapy were treated with fluconazole and showed a 97% clinical and mycological response [69]. A two-center RCT comparing amphotericin B with fluconazole for the treatment of fungal septicemia showed no difference in outcomes and a trend toward fewer side effects in the fluconazole group but was limited by a sample size of 23 infants and not powered to show differences in mortality or neurodevelopmental outcome. There have been no other clinical trials comparing the azoles with amphotericin in neonates.

Given the high morbidity and mortality associated with neonatal IC even in the face of appropriate therapy and the association of *Candida* colonization with subsequent IC [70–72], there has been considerable interest in fluconazole prophylaxis as a strategy to reduce the overall burden of IC in the nursery. To date there have been five randomized controlled trials (RCTs) [52, 65–68], eight retrospective reviews [19, 20, 73–78], and a Cochrane review [79] examining fluconazole prophylaxis in neonates.

The first of the RCT's was performed by Kicklighter, et al [67] and found that rectal colonization was significantly lower in VLBW infants receiving fluconazole 6 mg/kg/d versus placebo [15 vs. 46%, $p<0.001$]. In a prospective, randomized double-blind trial over a 30-month period of 100 infants with birth weights <1000 g, those infants who received fluconazole for 6 weeks had a decrease in fungal colonization (22% versus 60%) as well as a decrease in the development of invasive fungal infection compared to placebo (0% versus 20%) [65]. A prospective, randomized, double-blind trial by the same group comparing a twice weekly regimen with the regimen used in the previous study found no significant difference in fungal colonization ($p=0.83$) or invasive disease ($p=0.68$) [66]. A larger prospective, randomized double-blind, controlled trial conducted in 8 NICUs in Italy among 322 infants with birth weight <1500 g showed that a fluconazole prophylaxis regimen of 3 or 6 mg/kg every second day for 4–6 weeks significantly reduced the incidence of both *Candida* colonization [incidence of 9.8% in the 6 mg group, 7.7% in the 3 mg group, and 29.2% in the placebo group ($P<0.001$)] and invasive fungal infections [incidence of 2.7% in the 6 mg group ($P=0.005$), 3.8% in the 3 mg group ($P=0.02$), and 13.2% in the placebo group] [68]. In contrast to the other studies, Parikh et al [52] randomized 120 infants <1500 g to fluconazole prophylaxis 6 mg/kg/d every three days for the first week then daily for up to four weeks versus placebo. They found increased rates of fungal colonization in the placebo group [30% versus 8.3% ($p=0.003$)] but no difference in rate of IC [25% versus 26.7% ($p=0.835$)]. As opposed to most other reports in this population, *C. glabrata*, not *C. albicans*, was the dominant pathogen (71% versus 3.2%).

A Cochrane review meta-analysis of the five RCTs [79] showed a significantly lower incidence of invasive fungal infection in neonates treated with prophylactic fluconazole [relative risk 0.48 (95% CI 0.31, 0.73); number needed to treat (NNT): 11 (95% CI 7, 33)]. There was no significant difference in mortality between the fluconazole prophylaxis and placebo groups.

Use of a drug with limited data regarding dosing and safety in a vulnerable population such as premature neonates always involves weighing risks and benefits. Given the morbidity and mortality associated with invasive candidiasis and the number of fluconazole studies conducted to date, this drug is a possible choice for first line therapy. However, depending on local resistance patterns, other classes of antifungals (e.g. echinocandins, lipid-based amphotericin B formulations) might be better choices for first-line treatment due to their broader *Candida* spp coverage. In addition, fluconazole use in treatment is not recommended in settings where this drug is used routinely for prophylaxis. Related to this, the decision to use fluconazole for prophylaxis is more complicated and needs to carefully consider several variables. On one hand, exposing a large number of neonates to a drug for the benefit of a relative few is always a critical decision: in this view, evaluating the number-needed-to-treat is a correct approach. The prophylaxis studies above were conducted in centers with high baseline rates of candidemia [80]: obviously, in these centers there may be a solid benefit in adoption of prophylaxis. On the other hand, no clear benefit in reduction of mortality has been shown to date, and no assessment of the neurodevelopmental outcomes of premature neonates exposed to fluconazole is currently available. Pending this, universal prophylaxis cannot be recommended, but its use has to be considered on a center-to-center basis.

VORICONAZOLE

Voriconazole is a synthetic derivative of fluconazole. Voriconazole has the spectrum of activity of itraconazole, yet the bioavailability of fluconazole. Importantly, it has both fungicidal and fungistatic activity against *Aspergillus* [81–83].

Pharmacology

Voriconazole is available in both intravenous and oral formulations with approximately 90% oral bioavailability. It is extensively metabolized by the liver with less than 5% excreted unchanged in the urine. Voriconazole is 58% protein bound, has a large volume of distribution and penetrates well into the CSF. Dosing with 3–6mg/kg intravenously twice daily and 200mg orally twice daily results in serum trough concentrations of 2–6µg/ml and 2–3µg/ml respectively. Steady state concentrations for both intravenous and oral dosing are typically achieved after 5–6 days unless a loading dose is given in which case steady state concentrations are achieved in one day [84]. However, wide interpatient variability of drug exposure has been noted in adults following standard dosing.

There are several factors that are thought to contribute to this variability including nonlinear PK of voriconazole, genetic polymorphisms of CYP2C19, drug-drug interactions, liver disease, and patient age. Studies in both healthy volunteers [85–87] and critically ill adults [88, 89] have demonstrated non-linear PK that is thought to be due to saturable first-pass metabolism and decreased systemic clearance. Consequently small changes in dose may affect large changes in serum drug levels. Liver metabolism is primarily mediated by CYP2C19 of which several allelic polymorphisms have been identified. Individuals with poor metabolizing phenotypes have a roughly two-fold higher drug exposure than heterozygous extensive metabolizers and four-fold higher exposure than homozygous extensive metabolizers [90, 91]. Poor metabolizers may be found in up to 20% of non-Indian Asians while this trait is uncommon in white and black populations [84]. Like other azoles, voriconazole has the potential to interact with drugs metabolized by the CYP450 enzyme

system. Similarly, any liver injury affecting this metabolism has the potential to alter voriconazole drug exposure.

In contrast to adults, the PK of voriconazole in children is linear at lower doses and patient weight rather than age seems to play a larger role in determining drug exposure making extrapolation of adult data problematic. Based on PK/PD analysis in a prospective multicenter study of 39 immunocompromised children or children with documented invasive fungal disease age 2–11y, a dose of 4mg/kg intravenously was found to be equivalent to the recommended dose of 3mg/kg in adults [92]. Similar to adults, drug elimination correlated with CYP2C19 phenotype, but children were found to have higher elimination rates than those found in adults, which at least partially explains the linear kinetics at lower doses. In a population PK analysis of 3 open label pediatric studies involving 82 children 2–11 years of age, an intravenous dose of 7mg/kg or 200mg orally twice daily was found to be equivalent to adult dosing [92].

Toxicities, Side Effects, and Drug Interactions

Voriconazole's main side effects include reversible dose-dependent visual disturbances (increased brightness, blurred vision) in as many as one-third of treated patients [93, 94], elevated hepatic transaminases with increasing doses [95, 96], and occasional skin reactions likely due to photosensitization [81, 97–99].

As with other azoles the potential exists to modify the metabolism of other drugs, including a contraindication for concomitant use with sirolimus. In one study coadministration of voriconazole and tacrolimus elevated trough tacrolimus levels in one liver transplant patient nearly ten-fold [100], and in another study tacrolimus levels were significantly increased 2.2-fold when coadministered with voriconazole [101]. In a study of renal transplant patients, concomitant administration of voriconazole with cyclosporine also resulted in a 1.7-fold increase in the geometric mean for cyclosporine area under the plasma concentration-time curve, so it is recommended that the cyclosporine dose be halved and levels monitored frequently [102].

Clinical Studies in Adults

Voriconazole has been approved by the FDA as initial therapy for the treatment of invasive aspergillosis and candidemia [103]. The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis in adults showed better clinical response and improved survival in subjects receiving voriconazole versus those receiving amphotericin B deoxycholate [104]. A multicenter trial of voriconazole versus fluconazole in treating esophageal candidiasis in 391 immunocompromised patients showed similar success rates with voriconazole (98.3%) and fluconazole (95.1%) [105]. While overall safety and tolerability of both antifungals was acceptable in this study, fewer patients discontinued voriconazole than fluconazole due to poor clinical response, but more patients discontinued voriconazole because of laboratory abnormalities or adverse events.

Because of the non-linear PK in adults and high interpatient variability, investigators support voriconazole therapeutic drug monitoring to improve efficacy and limit toxicity. Studies in adults have shown that under-dosing voriconazole in patients with invasive fungal disease results in significant morbidity and mortality while high serum levels result in more frequent side effects [93, 94, 106–108]. In children the data are more limited. A recent retrospective study of 46 children aged 0.8–20.5 years showed that a trough concentration of 1 µg/mL was associated with increased survival and that serum levels based on a dosage of 7 mg/kg IV and 200mg oral twice daily were highly variable [109].

Pediatric Clinical Studies

The only pediatric-devoted study with voriconazole was an open-label evaluation of 58 children with a proven or probable invasive fungal infection who received voriconazole on a compassionate basis if they were refractory or intolerant to conventional antifungal therapies [110]. Most patients (72%) had aspergillosis, but the group also included scedosporiosis (14%), candidiasis (7%), and others. At the end of therapy (median duration 93 days), a total of 45% of children had a complete or partial response, and only 7% were discontinued from voriconazole because of intolerance. Stratifying outcome by pathogen revealed a complete or partial response of 43% against aspergillosis, 50% against candidemia, and 63% against scedosporiosis. The most commonly reported adverse events in these children included elevation in hepatic transaminases, skin rash and photosensitivity reaction, and abnormal vision.

The studies in neonates are limited to case reports. IV administered voriconazole has been used successfully in preterm infants of very low birth weight with primary cutaneous aspergillosis [111] and fluconazole-resistant *Candida albicans* [112]. Kohli et al [113] report successful use of oral voriconazole in two term newborns with cardiac disease. Voriconazole's known ocular side effects and concern over how it might affect the developing retina, make it unlikely that clinical trials are forthcoming in premature infants. Given the availability of other agents with better safety data in neonates (e.g. echinocandins [114–116], lipid-based amphotericin [117]), we recommend that voriconazole in this population is used only as salvage therapy for refractory fungal disease and for documented cases of cutaneous or invasive aspergillosis.

Therapeutic Drug Monitoring (TDM) of Voriconazole

Because of the non-linear PK observed in adults and high interpatient exposure variability, it is likely that voriconazole TDM will be implemented to improve efficacy and limit toxicity. Observational studies have noted therapeutic failure with voriconazole plasma levels $<1 \mu\text{g/ml}$ and increase in side effects when levels exceed $5\text{--}6 \mu\text{g/ml}$ [93, 107, 108, 118, 119]. Transient hepatotoxicity and visual disturbances are most commonly reported.[93, 94, 120] but serious neurological disturbances and liver failure have also been associated with levels $>5 \mu\text{g/ml}$ [106, 119].

Studies in children are more limited, but retrospective studies show that children also experience high interpatient variability in voriconazole concentrations [121] and that mortality decreases when voriconazole serum trough concentrations $>1 \mu\text{g/ml}$ are achieved [109]. Case studies in infants suggest that even higher voriconazole doses are needed to achieve this target trough concentration, underscoring the need for TDM [112, 122, 123]. Even though the data acquired thus far support the use of TDM, prospective studies are lacking in children and need to be conducted to answer this question. With increasing availability of voriconazole TDM in the clinical setting, practicing clinicians have an excellent tool with which to guide dosing in infants admitted to the nursery.

POSACONAZOLE

In September of 2006 the FDA approved posaconazole for the prophylaxis and treatment of disseminated candidiasis and aspergillosis in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis. Posaconazole is a second-generation triazole antifungal agent available as a suspension for oral administration. The antimicrobial spectrum of posaconazole is similar to voriconazole, but with additional activity against zygomycetes. Experience with posaconazole in children is very limited.

Pharmacology

Posaconazole is currently available only as an oral formulation and reaches maximum plasma concentrations 3 to 5 hours after ingestion. Dose proportional increases in plasma exposure (AUC) to posaconazole were observed following single oral doses from 50 mg to 800 mg and following multiple dose administration from 50 mg to 400 mg twice daily. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration [124]. When administered with a non-fat and high fat diet posaconazole exposure and maximum concentration are 3 to 4 times higher than with the fasting state [125]. In addition, posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors [126]. Posaconazole distributes well into tissues; is 98% protein bound; and is not a substrate for the cytochrome P-450 enzymatic system. However, about 20% of the parent drug is glucuronidated by phase 2 enzymes. Posaconazole is eliminated with a mean half-life of 25 hours (19–31 hours) with a total body clearance (CL/F) of 4.1 to 6.6 ml/min/kg [127]; it is predominantly eliminated in the feces with renal clearance playing a minor role. Therefore, no dose adjustment is necessary in mild to moderate renal insufficiency. Posaconazole is fungicidal *in vitro* with likely time-dependent killing [128].

Toxicities, Side Effects, and Drug Interactions

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers (i.e. rifabutin, phenytoin) of these clearance pathways may affect posaconazole plasma concentrations [129]. Posaconazole is also a CYP3A4 inhibitor and therefore, coadministration results in increased plasma concentrations of the following products: cyclosporine (75% dose reduction required), tacrolimus (60% dose reduction required), rifabutin, midazolam and phenytoin [129]. Similar to the other azoles, posaconazole causes transient hepatic reactions including mild to moderate elevations in ALT, AST, alkaline phosphatase, and total bilirubin [129].

Clinical Studies in Adults

In a multicenter (89 sites), international, randomized, single-blinded study of posaconazole (n=304) versus fluconazole or itraconazole (n=298) in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections [130]. Another multicenter, international, randomized, double-blinded study in patients with allogeneic hematopoietic stem-cell transplantation and graft versus hosts disease showed that posaconazole was not-inferior to fluconazole in the prevention of invasive fungal infections [130].

Pediatric Clinical Studies

In a study of 8 patients (7 pediatric patients 9 to 18 years of age) with chronic granulomatous disease and proven or possible invasive mould infection refractory to standard therapy, posaconazole (n=6, 400 mg orally twice per day; n=1, 200 mg orally three times per day) was well tolerated. Further, 6 of the 7 patients experienced complete resolution of infection [131]. Another report including data from 24 patients with active zygomycosis who were enrolled in two open-label, nonrandomized, multicentered compassionate trials that evaluated oral posaconazole as salvage therapy for invasive fungal infections showed that 2 children ages 7 and 17 years of age had partial response to posaconazole and 1 child age 18 had a complete response [132]. To our knowledge, there are no reports on the use of posaconazole in neonates, and we would only consider its use as salvage therapy.

RAVUCONAZOLE

Ravuconazole is structurally more similar to fluconazole and voriconazole, containing a thiazole instead of a second triazole. It is often fungicidal [133, 134], has 47–74% bioavailability with linear PK, and a long half-life of approximately 100 hours [135]. The drug is well-absorbed following oral administration, and its absorption is enhanced by food [134]. Penetration of ravuconazole into healthy rat tissue showed that concentration of drug in the lungs was 2–6 times higher than the corresponding blood concentration [136]. Ravuconazole has not been approved by the FDA.

Pharmacology

Ravuconazole is well tolerated, with headache a main side effect, and urine studies suggest no CYP isoenzyme induction [137]. Ravuconazole was also well-tolerated in healthy human subjects in single [135] and multiple doses [138]. Ravuconazole and coadministration with simvastatin was well-tolerated in 20 health subjects and showed ravuconazole was a less potent inhibitor of the CYP3A4 enzyme than other triazole antifungals [139]. Ravuconazole did not affect nelfinavir in 14 healthy volunteers [140].

Clinical Studies

A randomized trial of 76 patients with ravuconazole cured 76% of esophageal candidiasis patients 7 days after administration, with a safety profile similar to fluconazole [141]. A substudy analysis of HIV-positive patients with oropharyngeal candidiasis showed a 95% response rate after 5 days of therapy [142]. Ravuconazole was evaluated in a multicenter, phase I/II randomized, double-blind, placebo controlled trial, dose-ranging study of toenail onychomycosis. For 12 weeks participants (n=151) received one of the following dosing regimens: 200 mg/day; 100 mg/week; 400 mg/week or placebo. Clinical, microbiological cure, and clinical response was greater in those who received ravuconazole 200 mg/day [143].

Pediatric Clinical Studies

There are no clinical trials of ravuconazole in children, and we do not believe it currently has a role in the nursery.

TRIAZOLES AND EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal Membrane Oxygenation (ECMO) provides life-saving support for children with refractory cardiorespiratory failure. ECMO is a cardiopulmonary bypass device that provides complete respiratory and cardiac support and is used in intensive care units (ICU) when conventional modes of support have failed. Mechanically, blood is drained from the venous system, pumped through an artificial lung where oxygen is added and carbon dioxide removed, and then, depending on the configuration of the circuit, returned to either the venous or arterial circulation (Figure 1). ECMO has been used successfully in multiple pediatric disease states including meconium aspiration syndrome (MAS), acute respiratory distress syndrome (ARDS), pneumonia, post-cardiac surgery, post-heart and lung transplant with graft failure, fulminant myocarditis, and sepsis [144–149].

Children supported with ECMO are at high risk for nosocomial infections [150]. Risk factors for these infections include presence of large indwelling catheters, alterations in immune function, use of broad spectrum antibiotics, and frequent access of the ECMO circuit. The vast majority of pediatric patients on ECMO are covered with broad spectrum antibiotics, but antifungal use is much less consistent. In small epidemiological studies in ECMO patients, *Candida* spp are responsible for up to 50% of nosocomial infections [150–

153]. Since treatment of IC involves both antifungals and removal of indwelling catheters [154], in children on ECMO where removal of indwelling catheters is often clinically contraindicated, antifungal prophylaxis could potentially reduce the burden of disease.

There are relatively few studies evaluating the pharmacokinetics/ pharmacodynamics (PK/ PD) of drugs in patients on ECMO. However, the data suggest that the ECMO circuit can substantially alter the PK of antimicrobials resulting in changes to elimination and volume of distribution [155–163]. In addition, the critical condition of the patients in need of ECMO and the number of days on ECMO may further impact the PK changes observed.

No antifungals have been studied in any population of patients on ECMO. However, one *ex vivo* study using blood primed ECMO circuits demonstrated a dramatic decrease in voriconazole levels of 60% over 3 hours [157]. Since the circuit was not connected to a patient and the result was compared to a control specimen, drug loss was attributed to interactions between the drug and circuit [157]. Preliminary data from a phase 1 clinical trial investigating an IV fluconazole loading dose of 25mg/kg in children included one subject on ECMO [61]. While 72% of the subjects in this trial achieved the desired AUC_{0–24} of 400, the child on ECMO did not, suggesting the need for higher dosing in this population. A phase 1 clinical trial evaluating the PK/PD of fluconazole in children supported with ECMO is currently underway.

CONCLUSIONS

Infants in the NICU are at increased risk of invasive fungal disease. Management has evolved tremendously over the last decade with the azole antifungals playing a significant role. Areas for future research include the use of fluconazole for prophylaxis in vulnerable populations (e.g. VLBW infants and infants on ECMO) and to better delineate the PK/PD of the newer antifungals such as voriconazole, posaconazole, and ravuconazole.

Acknowledgments

Conflict of Interest/Funding Source:

Dr. Watt receives support from the United States Government for his work in pediatric research (5T32HD043029-09)

Dr. Cohen-Wolkowicz receives support from NICHD 1K23HD064814-01 and the Thrasher Research Fund for his work in pediatric clinical pharmacology and from Pfizer Inc. for neonatal and pediatric drug development.

Dr. Benjamin receives support from the United States Government for his work in pediatric and neonatal clinical pharmacology (1R01HD057956-02, 1R01FD003519-01, 1U10-HD45962-06, 1K24HD058735-01, and is the Principal Investigator of the Pediatric Trials Network, Government Contract HHSN275201000002I); the non profit organization Thrasher Research Foundation for his work in neonatal candidiasis (<http://www.thrasherresearch.org>); and from industry for neonatal and pediatric drug development (<http://www.dcri.duke.edu/research/coi.jsp>).

References

1. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, Lemons JA, Donovan EF, Stark AR, Tyson JE, Oh W, Bauer CR, Korones SB, Shankaran S, Laptook AR, Stevenson DK, Papile LA, Poole WK. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002; 110(2 Pt 1):285–291. [PubMed: 12165580]
2. Benjamin DK Jr, Stoll BJ. Infection in late preterm infants. *Clin. Perinatol*. 2006; 33(4):871–882. [PubMed: 17148010]
3. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, Duara S, Poole K, Laptook A, Goldberg R. National Institute of Child Health and Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors,

- mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics*. 2006; 117(1):84–92. [PubMed: 16396864]
4. Makhoul IR, Bental Y, Weisbrod M, Sujov P, Lusky A, Reichman B. Israel Neonatal Network. Candidal versus bacterial late-onset sepsis in very low birthweight infants in Israel: a national survey. *J Hosp. Infect.* 2007; 65(3):237–243. [PubMed: 17275963]
 5. Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. Invasive fungal infection in very low birthweight infants: national prospective surveillance study. *Arch. Dis. Child. Fetal Neonatal Ed.* 2006; 91(3):F188–F192. [PubMed: 16332924]
 6. Rodriguez D, Almirante B, Park BJ, Cuenca-Estrella M, Planes AM, Sanchez F, Gene A, Xercavins M, Fontanals D, Rodriguez-Tudela JL, Warnock DW, Pahissa A. Barcelona Candidemia Project Study Group. Candidemia in neonatal intensive care units: Barcelona, Spain. *Pediatr. Infect. Dis. J.* 2006; 25(3):224–229. [PubMed: 16511384]
 7. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of *Candida* bloodstream infections among NICU patients in the United States: 1995–2004. *Pediatrics*. 2006; 117(5):1680–1687. [PubMed: 16651324]
 8. Bartels DB, Schwab F, Geffers C, Poets CF, Gastmeier P. Nosocomial infection in small for gestational age newborns with birth weight <1500 g: a multicentre analysis. *Arch. Dis. Child. Fetal Neonatal Ed.* 2007; 92(6):F449–F453. [PubMed: 17460021]
 9. Friedman S, Richardson SE, Jacobs SE, O'Brien K. Systemic *Candida* infection in extremely low birth weight infants: short term morbidity and long term neurodevelopmental outcome. *Pediatr. Infect. Dis. J.* 2000; 19(6):499–504. [PubMed: 10877162]
 10. Lee BE, Cheung PY, Robinson JL, Evanochko C, Robertson CM. Comparative study of mortality and morbidity in premature infants (birth weight, < 1,250 g) with candidemia or candidal meningitis. *Clin. Infect. Dis.* 1998; 27(3):559–565. [PubMed: 9770157]
 11. Benjamin DK Jr, Ross K, McKinney RE Jr, Benjamin DK, Auten R, Fisher RG. When to suspect fungal infection in neonates: a clinical comparison of *Candida albicans* and *Candida parapsilosis* fungemia with coagulase-negative staphylococcal bacteremia. *Pediatrics*. 2000; 106(4):712–718. [PubMed: 11015513]
 12. Clerihew L, Lamagni TL, Brocklehurst P, McGuire W. *Candida parapsilosis* infection in very low birthweight infants. *Arch. Dis. Child. Fetal Neonatal Ed.* 2007; 92(2):F127–F129. [PubMed: 17337658]
 13. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin. Infect. Dis.* 1997; 24(6): 1122–1128. [PubMed: 9195068]
 14. Anaissie E, Bodey GP, Kantarjian H, David C, Barnett K, Bow E, Defelice R, Downs N, File T, Karam G. Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. *Am. J. Med.* 1991; 91(2):142–150. [PubMed: 1867240]
 15. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, Shadduck RK, Shea TC, Stiff P, Friedman DJ. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N. Engl. J. Med.* 1992; 326(13):845–851. [PubMed: 1542320]
 16. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. National Nosocomial Infections Surveillance System Hospitals. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. *Clin. Infect. Dis.* 2002; 35(5):627–630. [PubMed: 12173140]
 17. Bassetti M, Righi E, Costa A, Fasce R, Molinari MP, Rosso R, Pallavicini FB, Viscoli C. Epidemiological trends in nosocomial candidemia in intensive care. *BMC Infect. Dis.* 2006; 6:21. [PubMed: 16472387]
 18. Bassetti M, Ansaldi F, Nicolini L, Malfatto E, Molinari MP, Mussap M, Rebesco B, Bobbio Pallavicini F, Icardi G, Viscoli C. Incidence of candidaemia and relationship with fluconazole use in an intensive care unit. *J. Antimicrob. Chemother.* 2009; 64(3):625–629. [PubMed: 19622536]
 19. Healy CM, Baker CJ, Zaccaria E, Campbell JR. Impact of fluconazole prophylaxis on incidence and outcome of invasive candidiasis in a neonatal intensive care unit. *J. Pediatr.* 2005; 147(2):166–171. [PubMed: 16126043]

20. Healy CM, Campbell JR, Zaccaria E, Baker CJ. Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant *Candida* species. *Pediatrics*. 2008; 121(4):703–710. [PubMed: 18381534]
21. Manzoni P, Leonessa M, Galletto P, Latino MA, Arisio R, Maule M, Agriesti G, Gastaldo L, Gallo E, Mostert M, Farina D. Routine use of fluconazole prophylaxis in a neonatal intensive care unit does not select natively fluconazole-resistant *Candida* subspecies. *Pediatr. Infect. Dis. J.* 2008; 27(8):731–737. [PubMed: 18600191]
22. Benjamin DK Jr, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. *Pediatrics*. 2003; 112(3 Pt 1):634–640. [PubMed: 12949295]
23. Schelonka RL, Moser SA. Time to positive culture results in neonatal *Candida* septicemia. *J. Pediatr.* 2003; 142(5):564–565. [PubMed: 12756391]
24. Meis JF, Verweij PE. Current management of fungal infections. *Drugs*. 2001; 61(Suppl 1):13–25. [PubMed: 11219547]
25. Anaissie EJ, Darouiche RO, Abi-Said D, Uzun O, Mera J, Gentry LO, Williams T, Kontoyiannis DP, Karl CL, Bodey GP. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin. Infect. Dis.* 1996; 23(5):964–972. [PubMed: 8922787]
26. Rex JH, Bennett JE, Sugar AM, Pappas PG, van der Horst CM, Edwards JE, Washburn RG, Scheld WM, Karchmer AW, Dine AP. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *Candidemia Study Group and the National Institute. N. Engl. J. Med.* 1994; 331(20):1325–1330. [PubMed: 7935701]
27. Phillips JR, Karlowicz MG. Prevalence of *Candida* species in hospital-acquired urinary tract infections in a neonatal intensive care unit. *Pediatr. Infect. Dis. J.* 1997; 16(2):190–194. [PubMed: 9041599]
28. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. *J. Infect. Dis.* 2000; 181(1):309–316. [PubMed: 10608780]
29. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2009; 48(5):503–535. [PubMed: 19191635]
30. Perlroth J, Choi B, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. *Med. Mycol.* 2007; 45(4):321–346. [PubMed: 17510856]
31. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin. Microbiol. Rev.* 2007; 20(1):133–163. [PubMed: 17223626]
32. Riddell JT, Kauffman CA. The evolution of resistant *Candida* species in cancer centers: implications for treatment and prophylaxis. *Cancer*. 2008; 112(11):2334–2337. [PubMed: 18412152]
33. Spellberg BJ, Filler SG, Edwards JE Jr. Current treatment strategies for disseminated candidiasis. *Clin. Infect. Dis.* 2006; 42(2):244–251. [PubMed: 16355336]
34. Wilson AG, Micek ST, Ritchie DJ. A retrospective evaluation of fluconazole for the treatment of *Candida glabrata* fungemia. *Clin. Ther.* 2005; 27(8):1228–1237. [PubMed: 16199247]
35. Baddley JW, Patel M, Bhavnani SM, Moser SA, Andes DR. Association of fluconazole pharmacodynamics with mortality in patients with candidemia. *Antimicrob. Agents Chemother.* 2008; 52(9):3022–3028. [PubMed: 18591269]
36. Bilgen H, Ozek E, Korten V, Ener B, Molbay D. Treatment of systemic neonatal candidiasis with fluconazole. *Infection*. 1995; 23(6):394. [PubMed: 8655216]
37. Alexander BD, Schell WA, Miller JL, Long GD, Perfect JR. *Candida glabrata* fungemia in transplant patients receiving voriconazole after fluconazole. *Transplantation*. 2005; 80(6):868–871. [PubMed: 16210978]
38. Arendrup MC, Fuursted K, Gahrn-Hansen B, Schønheyder HC, Knudsen JD, Jensen IM, Bruun B, Christensen JJ, Johansen HK. Semi-national surveillance of fungaemia in Denmark 2004–2006:

- increasing incidence of fungaemia and numbers of isolates with reduced azole susceptibility. Clin. Microbiol. Infect. 2008; 14(5):487–494. [PubMed: 18294241]
39. Baddley JW, Smith AM, Moser SA, Pappas PG. Trends in frequency and susceptibilities of *Candida glabrata* bloodstream isolates at a university hospital. Diagn. Microbiol. Infect. Dis. 2001; 39(3):199–201. [PubMed: 11337190]
 40. Boschman CR, Bodnar UR, Tornatore MA, Obias AA, Noskin GA, Englund K, Postelnick MA, Suriano T, Peterson LR. Thirteen-year evolution of azole resistance in yeast isolates and prevalence of resistant strains carried by cancer patients at a large medical center. Antimicrob. Agents Chemother. 1998; 42(4):734–738. [PubMed: 9559774]
 41. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive candidiasis: *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. Cancer. 2008; 112(11):2493–2499. [PubMed: 18412153]
 42. Magill SS, Shields C, Sears CL, Choti M, Merz WG. Triazole cross-resistance among *Candida* spp.: case report, occurrence among bloodstream isolates, and implications for antifungal therapy. J. Clin. Microbiol. 2006; 44(2):529–535. [PubMed: 16455909]
 43. Magill SS, Swoboda SM, Shields CE, Colantuoni EA, Fothergill AW, Merz WG, Lipsett PA, Hendrix CW. The epidemiology of *Candida* colonization and invasive candidiasis in a surgical intensive care unit where fluconazole prophylaxis is utilized: follow-up to a randomized clinical trial. Ann. Surg. 2009; 249(4):657–665. [PubMed: 19300221]
 44. Nguyen MH, Peacock JE Jr, Morris AJ, Tanner DC, Nguyen ML, Snyderman DR, Wagener MM, Rinaldi MG, Yu VL. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. 1996; 100(6):617–623. [PubMed: 8678081]
 45. Panackal AA, Gribskov JL, Staab JF, Kirby KA, Rinaldi M, Marr KA. Clinical significance of azole antifungal drug cross-resistance in *Candida glabrata*. J. Clin. Microbiol. 2006; 44(5):1740–1743. [PubMed: 16672401]
 46. Pasqualotto AC, Zimmerman RA, Alves SH, Aquino VR, Branco D, Wiltgen D, do Amaral A, Cechinel R, Colares SM, da Rocha IG, Severo LC, Sukiennik TC. Take control over your fluconazole prescriptions: the growing importance of *Candida glabrata* as an agent of candidemia in Brazil. Infect. Control. Hosp. Epidemiol. 2008; 29(9):898–899. [PubMed: 18785850]
 47. Spanakis EK, Aperis G, Mylonakis E. New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage. Clin. Infect. Dis. 2006; 43(8):1060–1068. [PubMed: 16983621]
 48. Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Barton R, Bijie H, Bille J, Chang SC, da Luz Martins M, Duse A, Dzierzanowska D, Ellis D, Finquelievich J, Gould I, Gur D, Hoosen A, Lee K, Mallatova N, Mallie M, Peng NG, Petrikos G, Santiago A, Trupl J, VanDen Abeele AM, Wadula J, Zaidi M. Global Antifungal Surveillance Group. Geographic variation in the frequency of isolation and fluconazole and voriconazole susceptibilities of *Candida glabrata*: an assessment from the ARTEMIS DISK Global Antifungal Surveillance Program. Diagn. Microbiol. Infect. Dis. 2010; 67(2):162–171. [PubMed: 20338711]
 49. Pfaller MA, Messer SA, Boyken L, Tendolkar S, Hollis RJ, Diekema DJ. Variation in susceptibility of bloodstream isolates of *Candida glabrata* to fluconazole according to patient age and geographic location. J. Clin. Microbiol. 2003; 41(5):2176–2179. [PubMed: 12734273]
 50. Ruan SY, Lee LN, Jerng JS, Yu CJ, Hsueh PR. *Candida glabrata* fungaemia in intensive care units. Clin. Microbiol. Infect. 2008; 14(2):136–140. [PubMed: 18042196]
 51. Horn DL, Neofytos D, Anaissie EJ, Fishman JA, Steinbach WJ, Olyaei AJ, Marr KA, Pfaller MA, Chang CH, Webster KM. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin. Infect. Dis. 2009; 48(12):1695–1703. [PubMed: 19441981]
 52. Parikh TB, Nanavati RN, Patankar CV, Rao S, Bisure K, Udani RH, Mehta P. Fluconazole prophylaxis against fungal colonization and invasive fungal infection in very low birth weight infants. Indian Pediatr. 2007; 44(11):830–837. [PubMed: 18057479]
 53. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. Clin. Pharmacokinet. 1997; 33(1):52–77. [PubMed: 9250423]

54. Wildfeuer A, Laufen H, Schmalreck AF, Yeates RA, Zimmermann T. Fluconazole: comparison of pharmacokinetics, therapy and in vitro susceptibility. *Mycoses*. 1997; 40(7–8):259–265. [PubMed: 9476508]
55. Diflucan® package insert. New York: Roerig, a division of Pfizer, Inc.; 2008.
56. Klepser ME, Wolfe EJ, Jones RN, Nightingale CH, Pfaller MA. Antifungal pharmacodynamic characteristics of fluconazole and amphotericin B tested against *Candida albicans*. *Antimicrob. Agents Chemother.* 1997; 41(6):1392–1395. [PubMed: 9174207]
57. Ernst EJ, Klepser ME, Ernst ME, Messer SA, Pfaller MA. In vitro pharmacodynamic properties of MK-0991 determined by time-kill methods. *Diagn. Microbiol. Infect. Dis.* 1999; 33(2):75–80. [PubMed: 10091029]
58. Brammer KW, Coates PE. Pharmacokinetics of fluconazole in pediatric patients. *Eur. J. Clin. Microbiol. Infect. Dis.* 1994; 13(4):325–329. [PubMed: 8070441]
59. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clin. Pharmacokinet.* 1997; 33:52–77. [PubMed: 9250423]
60. Wade KC, Wu D, Kaufman DA, Ward RM, Benjamin DK Jr, Sullivan JE, Ramey N, Jayaraman B, Hoppu K, Adamson PC, Gastonguay MR, Barrett JS. National Institute of Child Health and Development Pediatric Pharmacology Research Unit Network. Population pharmacokinetics of fluconazole in young infants. *Antimicrob. Agents Chemother.* 2008; 52(11):4043–4049. [PubMed: 18809946]
61. Piper L, Smith PB, Hornik CP, Cheifetz IM, Barrett JS, Moorthy G, Hope WW, Wade KC, Cohen-Wolkowicz M, Benjamin DK Jr. Fluconazole loading dose pharmacokinetics and safety in infants. *Pediatr. Infect. Dis. J.* 2011; 30(5):375–378. [PubMed: 21085048]
62. Viscoli C, Castagnola E, Fioredda F, Ciravegna B, Barigione G, Terragna A. Fluconazole in the treatment of candidiasis in immunocompromised children. *Antimicrob. Agents Chemother.* 1991; 35:365–367. [PubMed: 2024968]
63. Schwarze R, Penk A, Pittrow L. Administration of fluconazole in children below 1 year of age. *Mycoses*. 1999; 42(1–2):3–16. [PubMed: 10394841]
64. Novelli V, Holzel H. Safety and tolerability of fluconazole in children. *Antimicrob. Agents Chemother.* 1999; 43(8):1955–1960. [PubMed: 10428919]
65. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N. Engl. J. Med.* 2001; 345(23):1660–1666. [PubMed: 11759644]
66. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. *J. Pediatr.* 2005; 147(2):172–179. [PubMed: 16126045]
67. Kicklighter SD, Springer SC, Cox T, Hulsey TC, Turner RB. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. *Pediatrics*. 2001; 107(2):293–298. [PubMed: 11158461]
68. Manzoni P, Stolfi I, Pugni L, Decembrino L, Magnani C, Vetrano G, Tridapalli E, Corona G, Giovannozzi C, Farina D, Arisio R, Merletti F, Maule M, Mosca F, Pedicino R, Stronati M, Mostert M, Gomirato G. Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N. Engl. J. Med.* 2007; 356(24):2483–2495. [PubMed: 17568029]
69. Fasano C, O'Keeffe J, Gibbs D. Fluconazole treatment of neonates and infants with severe fungal infections not treatable with conventional agents. *Eur. J. Clin. Microbiol. Infect. Dis.* 1994; 13(4): 351–354. [PubMed: 8070446]
70. Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, Miniero R, Gomirato G. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. *Pediatrics*. 2006; 118(6):2359–2364. [PubMed: 17142519]
71. Feja KN, Wu F, Roberts K, Loughrey M, Nesin M, Larson E, Della-Latta P, Haas J, Cimiotti J, Saiman L. Risk factors for candidemia in critically ill infants: a matched case-control study. *J. Pediatr.* 2005; 147(2):156–161. [PubMed: 16126040]

72. Saiman L, Ludington E, Pfaller M, Rangel-Frausto S, Wiblin RT, Dawson J, Blumberg HM, Patterson JE, Rinaldi M, Edwards JE, Wenzel RP, Jarvis W. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. *Pediatr. Infect. Dis. J.* 2000; 19(4):319–324. [PubMed: 10783022]
73. Aghai ZH, Mudduluru M, Nakhla TA, Amendolia B, Longo D, Kemble N, Kaki S, Sutsko R, Saslow JG, Stahl GE. Fluconazole prophylaxis in extremely low birth weight infants: association with cholestasis. *J. Perinatol.* 2006; 26(9):550–555. [PubMed: 16940972]
74. Bertini G, Perugi S, Dani C, Filippi L, Pratesi S, Rubaltelli FF. Fluconazole prophylaxis prevents invasive fungal infection in high-risk, very low birth weight infants. *J. Pediatr.* 2005; 147(2):162–165. [PubMed: 16126042]
75. Manzoni P, Arisio R, Mostert M, Leonessa M, Farina D, Latino MA, Gomirato G. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. *Pediatrics.* 2006; 117(1):e22–e32. [PubMed: 16326690]
76. McCrossan BA, McHenry E, O'Neill F, Ong G, Sweet DG. Selective fluconazole prophylaxis in high-risk babies to reduce invasive fungal infection. *Arch. Dis. Child. Fetal Neonatal Ed.* 2007; 92(6):F454–F458. [PubMed: 17460023]
77. Uko S, Soghier LM, Vega M, Marsh J, Reinersman GT, Herring L, Dave VA, Nafday S, Brion LP. Targeted short-term fluconazole prophylaxis among very low birth weight and extremely low birth weight infants. *Pediatrics.* 2006; 117(4):1243–1252. [PubMed: 16585321]
78. Weitkamp JH, Ozdas A, LaFleur B, Potts AL. Fluconazole prophylaxis for prevention of invasive fungal infections in targeted highest risk preterm infants limits drug exposure. *J. Perinatol.* 2008; 28(6):405–411. [PubMed: 18185518]
79. Clerihew L, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database Syst. Rev.* 2007; 4:CD003850. [PubMed: 17943803]
80. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr. National Institute for Child Health and Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics.* 2006; 118(2):717–722. [PubMed: 16882828]
81. Sabo JA, Abdel-Rahman SM. Voriconazole: a new triazole antifungal. *Ann Pharmacother.* 2000; 34:1032–1043. [PubMed: 10981251]
82. Manavathu EK, Cutright JL, Chandrasekar PH. In vitro susceptibility of itraconazole-resistant isolates of *Aspergillus fumigatus* to voriconazole. *Clin. Microbiol. Infect.* 1997; 3(Suppl 2):81.
83. Johnson EM, Szekely A, Warnock DW. In-vitro activity of voriconazole, itraconazole, and amphotericin B against filamentous fungi. *J. Antimicrob. Chemother.* 1998; 42:741–745. [PubMed: 10052897]
84. Johnson LB, Kauffman CA. Voriconazole: a new triazole antifungal agent. *Clin. Infect. Dis.* 2003; 36(5):630–637. [PubMed: 12594645]
85. Purkins L, Wood N, Ghahramani P, Greenhalgh K, Allen MJ, Kleinermans D. Pharmacokinetics and safety of voriconazole following intravenous- to oral-dose escalation regimens. *Antimicrob. Agents Chemother.* 2002; 46(8):2546–2553. [PubMed: 12121931]
86. Purkins L, Wood N, Greenhalgh K, Allen MJ, Oliver SD. Voriconazole, a novel wide-spectrum triazole: oral pharmacokinetics and safety. *Br. J. Clin. Pharmacol.* 2003; 56(Suppl 1):10–16. [PubMed: 14616408]
87. Patterson, BE.; Coates, PE. UK-109496, a novel, wide spectrum triazole derivative for the treatment of fungal infections: pharmacokinetics in man. Presented at: the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco, CA. 1995. Abstract F78
88. Myrianthefs P, Markantonis SL, Evaggelopoulos P, Despotelis S, Evodia E, Panidis D, Baltopoulos G. Monitoring plasma voriconazole levels following intravenous administration in critically ill patients: an observational study. *Int. J. Antimicrob. Agents.* 2010; 35(5):468–472. [PubMed: 20188523]

89. Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J. Clin. Pharmacol.* 2002; 42(4):395–402. [PubMed: 11936564]
90. Hyland R, Jones BC, Smith DA. Identification of the cytochrome P450 enzymes involved in the N-oxidation of voriconazole. *Drug Metab. Dispos.* 2003; 31(5):540–547. [PubMed: 12695341]
91. Ikeda Y, Umemura K, Kondo K, Sekiguchi K, Miyoshi S, Nakashima M. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. *Clin. Pharmacol. Ther.* 2004; 75(6):587–588. [PubMed: 15179414]
92. Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, Adamson P, Saez-Llorens X, Vora AJ, Arrieta AC, Blumer J, Lutsar I, Milligan P, Wood N. Pharmacokinetics and safety of intravenous voriconazole in children after single- or multiple-dose administration. *Antimicrob. Agents Chemother.* 2004; 48(6):2166–2172. [PubMed: 15155217]
93. Denning DW, Ribaud P, Milpied N, Caillot D, Herbrecht R, Thiel E, Haas A, Ruhnke M, Lode H. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin. Infect. Dis.* 2002; 34(5):563–571. [PubMed: 11807679]
94. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N. Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. *J. Clin. Pharmacol.* 2006; 46(2):235–243. [PubMed: 16432276]
95. Tan, KKC.; Brayshaw, N.; Oakes, M. Investigation of the relationship between plasma voriconazole concentrations and liver function test abnormalities in therapeutic trials. Presented at: the 41st Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Illinois. 2001.
96. Stone, J.; Holland, S.; Wickersham, P.; Deutsch, P.; Winchell, G.; Hesney, M.; Miller, R.; Freeman, A.; Dilzer, S.; Lasseter, K. Drug interactions between caspofungin and tacrolimus (abstract A-13). Presented at: the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Illinois. 2001.
97. Walsh TJ, Viviani MA, Arathoon E, Chiou C, Ghannoum M, Groll AH, Odds FC. New targets and delivery systems for antifungal therapy. *Med. Mycol.* 2000; 38(Suppl 1):335–347. [PubMed: 11204162]
98. Denning DW, Griffiths CEM. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. *Clin. Dermatol.* 2001; 26:648–653.
99. Gomez-Moyano E, Vera-Casafio A, Moreno-Perez D, Sanz-Trelles A, Crespo-Erchiga V. Lupus erythematosus-like lesions by voriconazole in an infant with chronic granulomatous disease. *Pediatr. Dermatol.* 2010; 27(1):105–106. [PubMed: 20199430]
100. Venkataramanan R, Zang S, Gayowski T, Singh N. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. *Antimicrob. Agents Chemother.* 2002; 46:3091–3093. [PubMed: 12183280]
101. Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants. *Cochrane Database Syst. Rev.* 2001; 2:CD002061. [PubMed: 11406029]
102. Romero AJ, Le Pogamp P, Nilsson LG, Wood N. Effect of voriconazole on the pharmacokinetics of cyclosporine in renal transplant patients. *Clin. Pharmacol. Ther.* 2002; 71:226–234. [PubMed: 11956505]
103. VFend® package insert. Pfizer Pharmaceuticals; New York: 2008.
104. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B. Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N. Engl. J. Med.* 2002; 347:408–415. [PubMed: 12167683]
105. Ally R, Schürmann D, Kreisel W, Carosi G, Aguirrebengoa K, Dupont B, Hodges M, Troke P, Romero AJ. Esophageal Candidiasis Study Group. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin. Infect. Dis.* 2001; 33:1447–1454. [PubMed: 11577374]

106. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin. Infect. Dis.* 2008; 46(2):201–211. [PubMed: 18171251]
107. Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG, Andes D. Voriconazole therapeutic drug monitoring. *Antimicrob. Agents Chemother.* 2006; 50(4):1570–1572. [PubMed: 16569888]
108. Trifilio S, Pennick G, Pi J, Zook J, Golf M, Kaniecki K, Singhal S, Williams S, Winter J, Tallman M, Gordon L, Frankfurt O, Evens A, Mehta J. Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. *Cancer.* 2007; 109(8):1532–1535. [PubMed: 17351937]
109. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. *Clin. Infect. Dis.* 2010; 50(1):27–36. [PubMed: 19951112]
110. Walsh TJ, Lutsar I, Driscoll T, Dupont B, Roden M, Ghahramani P, Hodges M, Groll AH, Perfect JR. Voriconazole in the treatment of aspergillosis, scedosporiosis and other invasive fungal infections in children. *Pediatr. Infect. Dis. J.* 2002; 21:240–248. [PubMed: 12005089]
111. Frankenbusch K, Eifinger F, Kribs A, Rengelshauseu J, Roth B. Severe primary cutaneous aspergillosis refractory to amphotericin B and the successful treatment with systemic voriconazole in two premature infants with extremely low birth weight. *J. Perinatol.* 2006; 26(8): 511–514. [PubMed: 16871222]
112. Muldrew KM, Maples HD, Stowe CD, Jacobs RF. Intravenous voriconazole therapy in a preterm infant. *Pharmacotherapy.* 2005; 25(6):893–898. [PubMed: 15927909]
113. Kohli V, Taneja V, Sachdev P, Joshi R. Voriconazole in newborns. *Indian Pediatr.* 2008; 45(3): 236–238. [PubMed: 18367773]
114. Benjamin DK Jr, Smith PB, Arrieta A, Castro L, Sánchez PJ, Kaufman D, Arnold LJ, Kovanda LL, Sawamoto T, Buell DN, Hope WW, Walsh TJ. Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin. Pharmacol. Ther.* 2010; 87(1):93–99. [PubMed: 19890251]
115. Sáez-Llorens X, Macias M, Maiya P, Píneros J, Jafri HS, Chatterjee A, Ruiz G, Raghavan J, Bradshaw SK, Kartsonis NA, Sun P, Strohmaier KM, Fallon M, Bi S, Stone JA, Chow JW. Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob. Agents Chemother.* 2009; 53(3):869–875. [PubMed: 19075070]
116. Cohen-Wolkowicz M, Benjamin DK Jr, Piper L, Cheifetz IM, Moran C, Liu P, Aram J, Kashuba AD, Capparelli E, Walsh TJ, Hope WW, Smith PB. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. *Clin. Pharmacol. Ther.* 2011; 89(5):702–707. [PubMed: 21412233]
117. Linder N, Klinger G, Shalit I, Levy I, Ashkenazi S, Haski G, Levit O, Sirota L. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. *J. Antimicrob. Chemother.* 2003; 52(4):663–667. [PubMed: 12972450]
118. Boyd AE, Modi S, Howard SJ, Moore CB, Keevil BG, Denning DW. Adverse reactions to voriconazole. *Clin. Infect. Dis.* 2004; 39(8):1241–1244. [PubMed: 15486850]
119. Imhof A, Schaer DJ, Schanz U, Schwarz U. Neurological adverse events to voriconazole: evidence for therapeutic drug monitoring. *Swiss Med. Wkly.* 2006; 136(45–46):739–742. [PubMed: 17183438]
120. Matsumoto K, Ikawa K, Abematsu K, Fukunaga N, Nishida K, Fukamizu T, Shimodozono Y, Morikawa N, Takeda Y, Yamada K. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. *Int. J. Antimicrob. Agents.* 2009; 34(1):91–94. [PubMed: 19261446]
121. Pasqualotto AC, Shah M, Wynn R, Denning DW. Voriconazole plasma monitoring. *Arch. Dis. Child.* 2008; 93(7):578–581. [PubMed: 18252755]
122. Santos RP, Sánchez PJ, Mejias A, Benjamin DK Jr, Walsh TJ, Patel S, Jafri HS. Successful medical treatment of cutaneous aspergillosis in a premature infant using liposomal amphotericin B, voriconazole and micafungin. *Pediatr. Infect. Dis. J.* 2007; 26(4):364–366. [PubMed: 17414408]

123. Maples HD, Stowe CD, Saccente SL, Jacobs RF. Voriconazole serum concentrations in an infant treated for *Trichosporon beigeli* infection. *Pediatr. Infect. Dis. J.* 2003; 22(11):1022–1024. [PubMed: 14628778]
124. Courtney R, Pai S, Laughlin M, Lim J, Batra V. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. *Antimicrob. Agents Chemother.* 2003; 47(9):2788–2795. [PubMed: 12936975]
125. Courtney R, Wexler D, Radwanski E, Lim J, Laughlin M. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. *Br. J. Clin. Pharmacol.* 2004; 57(2):218–222. [PubMed: 14748822]
126. Krishna G, Moton A, Ma L, Medlock MM, McLeod J. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. *Antimicrob. Agents Chemother.* 2009; 53(3):958–966. [PubMed: 19075045]
127. Courtney R, Sansone A, Smith W, Marbury T, Statkevich P, Martinho M, Laughlin M, Swan S. Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease. *J. Clin. Pharmacol.* 2005; 45:185–192. [PubMed: 15647411]
128. Groll AH, Mickiene D, Petraitis V, Petraitiene R, Ibrahim KH, Piscitelli SC, Bekersky I, Walsh TJ. Compartmental pharmacokinetics and tissue distribution of the antifungal echinocandin lipopeptide micafungin (FK463) in rabbits. *Antimicrob. Agents Chemother.* 2001; 45(12):3322–3327. [PubMed: 11709303]
129. Schiller DS, Fung HB. Posaconazole: an extended-spectrum triazole antifungal agent. *Clin. Ther.* 2007; 29(9):1862–1886. [PubMed: 18035188]
130. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N. Engl. J. Med.* 2007; 356(4):348–359. [PubMed: 17251531]
131. Segal BH, Barnhart LA, Anderson VL, Walsh TJ, Malech HL, Holland SM. Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin. Infect. Dis.* 2005; 40(11):1684–1688. [PubMed: 15889369]
132. Greenberg RN, Mullane K, van Burik JA, Raad I, Abzug MJ, Anstead G, Herbrecht R, Langston A, Marr KA, Schiller G, Schuster M, Wingard JR, Gonzalez CE, Revankar SG, Corcoran G, Kryscio RJ, Hare R. Posaconazole as salvage therapy for zygomycosis. *Antimicrob. Agents Chemother.* 2006; 50(1):126–133. [PubMed: 16377677]
133. Moore CB, Walls CM, Denning DW. In vitro activity of the new triazole BMS-207147 against *Aspergillus* species in comparison with itraconazole and amphotericin B. *Antimicrob. Agents Chemother.* 2000; 44:441–443. [PubMed: 10639380]
134. Arian S, Rex JH. Ravuconazole. *Curr. Opin. Investig. Drugs.* 2002; 3:555–561.
135. Olsen, SJ.; Mummaneni, V.; Rolan, P.; Norton, J.; Grasela, DM. Ravuconazole single ascending oral dose study in healthy subjects. Presented at: 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada. Abstract 838
136. Mikamo H, Yin XH, Hayasaki Y, Shimamura Y, Uesugi K, Fukayama N, Satoh M, Tamaya T. Penetration of ravuconazole, a new triazole antifungal, into rat tissues. *Chemotherapy.* 2002; 48:7–9. [PubMed: 11901249]
137. Ernst EJ. Investigational antifungal agents. *Pharmacotherapy.* 2001; 21:165S–175S. [PubMed: 11501989]
138. Faix RG, Polley TZ, Grasela TH. A randomized, controlled trial of parenteral clindamycin in neonatal necrotizing enterocolitis. *J. Pediatr.* 1988; 112(2):271–277. [PubMed: 3276864]
139. Mummaneni, V.; Gerald, M.; Hadjilambris, O.; Ouyang, Z.; Uderman, U.; Marino, M. Effect of ravuconazole on the pharmacokinetics of simvastatin in healthy subjects. Presented at: the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada.
140. Mummaneni, V.; Hadjilambris, OW.; Nichola, P.; Yan, J.; Salahudeen, I.; Marino, M. Ravuconazole does not affect the pharmacokinetics of nelfinavir [abstract A-25]. Presented at: the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16–19, 2001; Chicago, Illinois.

141. Beale, M.; Queiroz-Telles, F.; Banhegyi, D.; Li, N.; Pierce, PF. Randomized, double-blind study of the safety and antifungal activity of ravuconazole relative to fluconazole in esophageal candidiasis. Presented at: the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16–19, 2001; Chicago, Illinois.
142. Sakarcan A, Tenney F, Wilson JT, Stewart JJ, Adcock KG, Wells TG, Vachharajani NN, Hadjilambiris OW, Slugg P, Ford NF, Marino MR. The pharmacokinetics of irbesartan in hypertensive children and adolescents. *J. Clin. Pharmacol.* 2001; 41(7):742–749. [PubMed: 11452706]
143. Gupta AK, Leonardi C, Stoltz RR, Pierce PF, Conetta B. Ravuconazole Onychomycosis Group. A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. *J. Eur. Acad. Dermatol. Venereol.* 2005; 19(4):437–443. [PubMed: 15987289]
144. Fischer S, Bohn D, Rycus P, Pierre AF, de Perrot M, Waddell TK, Keshavjee S. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. *J. Heart Lung Transplant.* 2007; 26(5):472–477. [PubMed: 17449416]
145. Meyer DM, Jessen ME. Results of extracorporeal membrane oxygenation in children with sepsis. The Extracorporeal Life Support Organization. *Ann. Thorac. Surg.* 1997; 63(3):756–761. [PubMed: 9066397]
146. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. *Crit. Care Med.* 1996; 24(2):323–329. [PubMed: 8605808]
147. Lequier L. Extracorporeal life support in pediatric and neonatal critical care: a review. *J. Intensive Care Med.* 2004; 19(5):243–258. [PubMed: 15358943]
148. Frenckner B, Radell P. Respiratory failure and extracorporeal membrane oxygenation. *Semin. Pediatr. Surg.* 2008; 17(1):34–41. [PubMed: 18158140]
149. Rajagopal SK, Almond CS, Laussen PC, Rycus PT, Wypij D, Thiagarajan RR. Extracorporeal membrane oxygenation for the support of infants, children, and young adults with acute myocarditis: a review of the Extracorporeal Life Support Organization registry. *Crit. Care Med.* 2010; 38(2):382–387. [PubMed: 19789437]
150. O'Neill JM, Schutze GE, Heulitt MJ, Simpson PM, Taylor BJ. Nosocomial infections during extracorporeal membrane oxygenation. *Intensive Care Med.* 2001; 27(8):1247–1253. [PubMed: 11511935]
151. Zach TL, Steinhorn RH, Georgieff MK, Mills MM, Green TP. Leukopenia associated with extracorporeal membrane oxygenation in newborn infants. *J. Pediatr.* 1990; 116(3):440–444. [PubMed: 2308038]
152. Schutze GE, Heulitt MJ. Infections during extracorporeal life support. *J. Pediatr. Surg.* 1995; 30(6):809–812. [PubMed: 7666312]
153. Hsu MS, Chiu KM, Huang YT, Kao KL, Chu SH, Liao CH. Risk factors for nosocomial infection during extracorporeal membrane oxygenation. *J. Hosp. Infect.* 2009; 73(3):210–216. [PubMed: 19782430]
154. Eppes SC, Troutman JL, Gutman LT. Outcome of treatment of candidemia in children whose central catheters were removed or retained. *Pediatr. Infect. Dis. J.* 1989; 8(2):99–104. [PubMed: 2704608]
155. Amaker RD, DiPiro JT, Bhatia J. Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation. *Antimicrob. Agents Chemother.* 1996; 40(5): 1139–1142. [PubMed: 8723454]
156. Hoie EB, Swigart SA, Leuschen MP, Willett LD, Bolam DL, Goodrich PD, Bussey ME, Nelson RM Jr. Vancomycin pharmacokinetics in infants undergoing extracorporeal membrane oxygenation. *Clin. Pharm.* 1990; 9(9):711–715. [PubMed: 2225752]
157. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH. Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. *Intensive Care Med.* 2007; 33(6):1018–1024. [PubMed: 17404709]

158. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. *Clin. Pharmacokinet.* 2003; 42(5):403–417. [PubMed: 12739981]
159. Bhatt-Mehta V, Johnson CE, Schumacher RE. Gentamicin pharmacokinetics in term neonates receiving extracorporeal membrane oxygenation. *Pharmacotherapy.* 1992; 12(1):28–32. [PubMed: 1549536]
160. Cohen P, Collart L, Prober CG, Fischer AF, Blaschke TF. Gentamicin pharmacokinetics in neonates undergoing extracorporeal membrane oxygenation. *Pediatr. Infect. Dis. J.* 1990; 9(8): 562–566. [PubMed: 2122409]
161. Dodge WF, Jelliffe RW, Zwischenberger JB, Bellanger RA, Hokanson JA, Snodgrass WR. Population pharmacokinetic models: effect of explicit versus assumed constant serum concentration assay error patterns upon parameter values of gentamicin in infants on and off extracorporeal membrane oxygenation. *Ther. Drug Monit.* 1994; 16(6):552–599. [PubMed: 7878693]
162. Munzenberger PJ, Massoud N. Pharmacokinetics of gentamicin in neonatal patients supported with extracorporeal membrane oxygenation. *ASAIO Trans.* 1991; 37(1):16–18. [PubMed: 2012712]
163. Southgate WM, DiPiro JT, Robertson AF. Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. *Antimicrob. Agents Chemother.* 1989; 33(6):817–819. [PubMed: 2764529]

Figure 1.
Schematic of ECMO circuit.