Original Article

Initial use of voriconazole positively affects outcome of *Candida parapsilosis* bloodstream infection: a retrospective analysis

Yejuan Wu, Dong Wei, Xiaohui Gong, Yunlin Shen, Yingying Zhu, Junfang Wang, Zhen Gao

Department of Neonatology, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai, China

Contributions: (I) Conception and design: Y Wu, X Gong; (II) Administrative support: X Gong; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: Y Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiaohui Gong. Department of Neonatology, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai 200062, China. Email: gongxh@shchildren.com.cn.

Background: Concerns have arisen regarding the optimal antifungal regimen for *Candida parapsilosis* (*C. parapsilosis*) bloodstream infection (BSI) in view of its reduced sensitivity to fluconazole.

Methods: The clinical characteristics of 58 *C. parapsilosis* BSI newborns who received treatment between June 2014 to December 2018 in the Shanghai Children's Hospital were retrospectively analyzed. Based on the initial antifungal drugs, these patients were divided into fluconazole group (n=30) and voriconazole group (n=21). After 7–10-day treatment, the antifungal drugs were replaced if blood culture still showed positive. The clinical characteristics and therapeutic effects were compared between two groups.

Results: There were no significant differences in the clinical characteristics between two groups (P>0.05). The median time to a negative culture in the voriconazole group was 7 [interquartile range (IQR), 6–10] days, which was significantly shorter than in the fluconazole group [9 (IQR, 7–18.5) days; P=0.034]. The overall median time to a negative culture was 8 days. After 8-day antifungal therapy, in the voriconazole group and fluconazole group, negative culture was observed in 16 and 12 patients, respectively; the positive culture was noted in 5 and 16 patients, respectively; the effective rate was 76.1% and 40%, respectively, showing marked difference (χ^2=6.535, P=0.011). None died in the voriconazole group, but 4 died in the fluconazole group. The median time of treatment for fungal sepsis in the voriconazole group was 22 (IQR, 20–26) days, which was significantly shorter than in the fluconazole group [32 (IQR, 23.5–40) days; P=0.000].

Conclusions: The initial clinical manifestations of *C. parapsilosis* BSI vary among individuals, and voriconazole is superior to fluconazole in the treatment of *C. parapsilosis* BSI.

Keywords: *Candida parapsilosis*; fungal sepsis; fluconazole; voriconazole; treatment

Submitted Jan 18, 2020. Accepted for publication Jul 05, 2020.

doi: 10.21037/tp-20-37

View this article at: http://dx.doi.org/10.21037/tp-20-37

Introduction

Over the past 2 decades, *Candida parapsilosis* (*C. parapsilosis*) has become the second or the third most common *Candida* species from blood cultures worldwide and *C. parapsilosis* infection has been a persistent public health problem with great impact on the health care-associated costs and attributable mortality (1,2). In the UK and North America, *Candida* species accounts for more than 1/4 of all invasive fungal infections in low birth weight infants and *Candida* species infection has been a leading cause of neonatal mortality (3). Available studies have revealed the important differences among non-albicans species and *Candida albicans* (*C. albicans*), challenging the notion that lessons learned from study of *C. albicans* will be broadly applicable to other pathogenic *Candida*.

Fluconazole is generally effective for the treatment of candidaemia/invasive candidiasis (C/IC), but its wide use in

clinical practice may be hampered by a potential increase in the infection of fluconazole-resistant *Candida spp*. (4-6).

It is difficult to investigate the optimal therapy for *C. parapsilosis* complex infection in randomized controlled clinical trials, and well-designed observational studies become important sources of findings on the therapy of *C. parapsilosis* complex infection. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-37).

Methods

Population

A total of 58 newborn infants with *C. parapsilosis* bloodstream infection (BSI) were admitted to the Department of Neonatal Pediatrics of Shanghai Children's Hospital between 2014 and 2018, and these patients were included for retrospective analysis. There were 33 males and 25 females; 37 were born by cesarean section and 21 by natural delivery; the average gestational age was 32.6±3.5 weeks (range, 27–42 weeks) and the average birth weight was 1,869±836 g (range, 860–3,850 g). In addition, there were 6 full-term infants and 52 premature infants; 22 patients had very low birth weight and 6 had extreme low birth weight. The maternal diseases were as follows: premature rupture of membranes (n=16), gestational diabetes (n=7), gestational hypertension with or without eclampsia (n=8), Hashimoto thyroiditis (n=1), hypothyroidism (n=1) and gestational diabetes with hyperthyroidism (n=1).

Exclusion criteria were as follows: refusal of anti-fungal therapy (n=7): severe ischemic hypoxic encephalopathy complicated with epilepsy (n=2), recurrent bacterial pneumonia (n=1), severe suffocation (n=1), central hypopnea syndrome (n=1), neonatal necrotizing enterocolitis (NEC) with intestinal stenosis (n=1), bacterial septic shock (n=1).

The diagnostic criteria for fungal septicemia in neonates were as follows (7): (I) the culture of venous blood samples collected from at least 2 different sites showed *C. albicans*; (II) patients had clinical characteristics of sepsis, including changes in body temperature, feeding intolerance, weight loss, apnea and other manifestations.

According to the initial antifungal drugs used, the patients were divided into fluconazole group (n=30) and voriconazole group (n=21); after 7–10-day treatment, the anti-fungal drugs were replaced if blood fungal culture still showed positive. Fluconazole was intravenously administered at 12 mg/kg/dose, once daily, and voriconazole was intravenously administered at 7 mg/kg/dose, twice daily. Treatment continued for 2 weeks after blood culture showed negative. In the fluconazole group, 20 received voriconazole treatment after blood culture showed still positive following fluconazole treatment for 7–10-day, and the protocol of voriconazole treatment was above mentioned. In the case of fungal infection of central nervous system or other sites, the course of treatment was 4–12 weeks longer. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Shanghai Children's Hospital (NO.: 2020R046-E01) and informed consent was taken from all the patients.

Methodology

The clinical characteristics (such as gestational age, birth weight, obstetric conditions, clinical symptoms at onset, high-risk factors, clinical manifestations and complications) were collected based on medical records and compared between two groups. The time to blood culture showing negative, time of treatment for fungal sepsis, and the ratio of blood culture showing negative within 8 days after treatment were determined and compared between two groups.

Drug sensitive test

CLS (M27-A) protocol was used to determine the sensitivity to amphotericin B (AmB), fluconazole, 5-fluorocytosine (5-Fc), voriconazole, micafungin (MCF) and itraconazole (ICZ) by determining the minimum inhibitory concentration (MIC). The drug sensitivity was assessed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and American Clinical and Laboratory Standards Institute (CLSI) criteria (8).

Statistical analysis

Statistical analysis was done using SPSS version 23. Continuous data with a normal distribution are expressed as mean ± standard deviation (SD) and compared with t-test. The data with non-normal distribution are expressed as median and interquartile range (IQR), and compared with non-parametric analysis. Categorical data are expressed as frequencies and percentages, and compared with Chi-square (χ^2) test. A value of $P<0.05$ was considered statistically significant.

Table 1 General demographic characteristics of patients in two groups

Characteristics	Fluconazole (n=30)	Voriconazole (n=21)	χ^2/Z	P value
Sex (male/female)	17/13	12/9	0.001	0.973
Age in days, median [IQR]	0.17 [0.13, 1.00]	0.13 [0.08, 0.23]	2.080	0.149
Gestational age (weeks), median [IQR]	32.14 [31.00, 34.78]	31.71 [29.78, 32.67]	1.874	0.171
Birth weight (g), median [IQR]	1,755.0 [1,437.5, 2,147.5]	1,605.0 [1,222.5, 1,867.5]	2.286	0.131
Cesarean delivery, n (%)	21 (70.0)	13 (61.9)	0.364	0.546
Gestational diabetes, n (%)	4 (13.3)	2 (9.5)	0.000	1.000
Gestational hypertension, n (%)	3 (10.0)	5 (23.8)	0.890	0.345
Asphyxia, n (%)	9 (30.0)	5 (23.8)	0.238	0.626
Premature rupture of membranes, n (%)	8 (26.7)	6 (28.6)	0.023	0.881

IQR, interquartile range.

Results

General demographic characteristics

There were no significant differences in the general demographic characteristics (gender/age in days/gestational age/weight), maternal and intrapartum factors (delivery method/gestational diabetes/gestational hypertension/asphyxia/premature rupture of membranes) between voriconazole group and fluconazole group (P>0.05) (*Table 1*).

Clinical manifestations

There were no significant differences in the clinical manifestations at onset (fever/apnea/feeding intolerance), laboratory findings [granulocyte reduction/C-reactive protein (CRP) increase/blood platelet count (BPC) reduction/hepatic dysfunction/electrolyte abnormality/fungal meningitis/shock/coagulation abnormality/gastrointestinal diseases/neonatal respiratory distress syndrome (NRDS)/bronchopulmonary dysplasia (BPD)/patent ductus arteriosus (PDA)] and imaging findings (cranial imaging) between two groups (P>0.05).

Baseline diseases were as follows: perinatal asphyxia (n=13), NRDS (n=24), neonatal NEC (n=7), congenital megacolon (n=3), jejunal volvulus (n=1), ileum perforation (n=1), congenital intestinal malrotation (n=1), and congenital esophageal atresia (n=1). There were no marked differences in these diseases between two groups (P>0.05).

Potential risk factors for fungal septicaemia were as follows: intravenous nutrition (n=51), broad-spectrum antibiotics (35/51; 68.6%), endotracheal intubation (14/51; 27.5%), central venous catheterization (29/51; 56.9%), and prenatal dexamethasone (14/51; 27.5%). There were no marked differences between two groups in these factors (P>0.05). Fundus examination showed slightly retinal vein tortuosity in 2 cases and arterial narrowing in 2 cases (*Table 2*).

The drug sensitivity examination showed the MIC was <0.062 μg/mL for voriconazole, <0.5 μg/mL for AmB, <1 μg/mL for fluconazole, <4 μg/mL for 5-Fc, <0.125 μg/mL for ICZ, and <2 μg/mL for MCF. This suggested that *C. parapsilosis* was sensitive to these drugs.

Treatment results

The median time to blood culture showing negative was 7 (IQR, 6–10) days in the voriconazole group, which was significantly shorter than in the fluconazole group [9 (IQR, 7–18.5) days, P=0.034]. The overall median time negative blood culture was 8 days. After 8-day antifungal therapy, the negative blood culture was noted in 16 patients and positive blood culture in 5 patients in the voriconazole group, with effective rate of 76.1%. In the fluconazole group, the negative blood culture was found in 12 patients and positive blood culture in 16, with the effective rate of 40%. The proportion of patients with negative blood culture in the voriconazole group was significantly higher than in the fluconazole group (χ^2=6.535, P=0.011). None died in the voriconazole group but 4 deaths were observed in the fluconazole group (*Table 3*).

The median time of treatment for fungal sepsis was 22 (IQR, 20–26) days in the voriconazole group, which was

Table 2 Clinical characteristics of patients in two groups

Characteristics	Fluconazole (n=30)	Voriconazole (n=21)	χ^2/Z	P value
Risk factors				
PICC	18 (60.0)	11 (52.4)	0.292	0.589
Endotracheal intubation	10 (33.3)	4 (19.0)	0.650	0.420
Corticosteroids	8 (26.7)	6 (28.6)	0.023	0.881
PN	30 (100.0)	21 (100.0)	–	–
Broad-spectrum antibiotic	22 (73.3)	13 (61.9)	0.749	0.387
Manifestations of onset				
Fever	10 (33.3)	10 (47.6)	1.058	0.304
Apnea	10 (33.3)	11 (52.4)	1.850	0.174
Feeding intolerance	5 (16.7)	6 (28.6)	1.035	0.309
Clinical manifestations				
Time of blood culture negative (d), median [IQR]	9 [7, 18.5]	7 [6, 10]	4.516	0.034
Granulocyte reduce	15 (50.0)	13 (61.9)	0.707	0.400
CRP rise	28 (93.3)	19 (90.5)	0.000	1.000
BPC down	16 (53.3)	10 (47.6)	0.161	0.688
Liver function abnormal	20 (66.7)	10 (47.6)	1.850	0.174
Electrolyte abnormal	7 (23.3)	5 (23.8)	0.002	0.969
Head image abnormal	7 (23.3)	5 (23.8)	0.002	0.969
Fungal meningitis	3 (10.0)	2 (9.5)	0.000	1.000
Shock	8 (26.7)	4 (19.0)	0.088	0.767
Coagulation abnormal	5 (16.7)	1 (4.8))	0.735	0.391
Intestinal disease	10 (33.3)	4 (19.0)	0.650	0.420
NRDS	12 (40.0)	12 (57.1)	1.457	0.227
BPD	1 (3.3)	3 (14.3)	0.815	0.367
PDA	14 (46.7)	5 (23.8)	2.761	0.097

PICC, peripherally inserted central catheter; PN, parenteral nutrition; IQR, interquartile range; CRP, C-reactive protein; BPC, blood platelet count; NRDS, neonatal respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus.

Table 3 Time to negative blood culture in two groups (number of patients)

Treatment	Effective	Invalid	Total	RR (%)
Fluconazole	12	18	30	40.0
Voriconazole	16	5	21	76.2
Total	28	23	51	54.9

RR, response rate.

Table 4 Time of treatment for fungal sepsis in two groups (days)

Treatment	Median [IQR]
Fluconazole (n=25)	32 [23.5, 40]
Voriconazole (n=19)	22 [20, 26]
Z	−20.219
P	0.000

Note: fungal meningitis patients were excluded in both groups, including 3 in the fluconazole group and 2 in the voriconazole group. Two deaths were excluded in the fluconazole group before the end of antifungal therapy. IQR, interquartile range.

significantly shorter than in the fluconazole group [32 (IQR, 23.5–40) days; P=0.000] (*Table 4*).

Discussion

Fungal BSI is an important morbidity in neonates with the mortality ranging from 21% to 76% (9,10). The candidaemia accounts for 30–50% of causes of fungal BSI related death, which is significantly higher than that reported after most bacterial infections (11). *C. albicans* is the most common fungus, followed by *C. parapsilosis*. In recent years, the incidence of infection caused by C. tropicalis and C. glabrata is increasing. Recent studies have reported that *C. parapsilosis* has become the first or second cause of candidaemia in the Latin America, Asia and Europe (12-15).

C. parapsilosis is a commensal fungus in the human skin and it has been widely understood because of its potent ability to form biofilms on the indwelling devices such as central venous catheters. Recent studies have also highlighted the importance of fatty acid synthesis and storage in the pathogenesis of *C. parapsilosis* infection. The incidence of *C. parapsilosis* infection in neonates is significantly higher than in other high-risk populations. This suggests a unique susceptibility of neonates to *C. parapsilosis* infection. In the neonatal intensive care unit (NICU), the risk factors for the development of invasive candidiasis infection include very low birth weight, parenteral nutrition, use of central catheters, abdominal surgery, NEC, mechanical ventilation, endotracheal intubation, and exposure to broad-spectrum antibiotics/steroids (11,16-19). Fungal colonization is an important predisposing factor for developing invasive disease (20). Of note, the *C. parapsilosis* colonization is several weeks later than the *C. albicans* colonization in neonates (21), which is consistent with fact that *C. parapsilosis* is a rare cause of early-onset sepsis in neonates.

Early diagnosis and aggressive treatment improve the outcome of fungal BSI, which is mainly based on isolation of predominant fungus and drug sensitivity test. The symptoms of suspected fungal BSI include fever, lethargy, thrombocytopenia, glucose instability, feeding intolerance, increased requirement for mechanical ventilation and apnoea. Our results showed the symptoms of suspected *C. parapsilosis* BSI varied among individuals and were characterized by fever (27.4%), apnea (25.5%) and abdominal distension (27.4%).

The treatments of candidemia and other infections of invasive candidiasis is still a challenge in clinical practice. The most common first-line treatment is fluconazole, followed by lipid formulation AmB, caspofungin, voriconazole and other antifungal drugs. The prophylactic use of fluconazole is still controversial (22-24). In the present study, the incidence of fluconazole resistance was high in the initial treatment of *C. parapsilosis* infection with fluconazole. A recent study found that more *C. parapsilosis* were resistant to fluconazole as compared to *C. albicans* (16/32 *vs.* 1/16, P<0.003 Fisher exact test) (25). AmB deoxycholate is the second most commonly used antifungal drug. In the 2016 America guideline for the management of candidiasis, AmB deoxycholate (1 mg/kg/d) is recommended for the treatment of disseminated candidiasis in neonates. Limited evidence shows the lipid formulation of AmB is preferred because of its high toxicity (26,27). This guideline also recommends the initial treatment of candidiasis with echinomycin antifungal drugs, but these antifungal drugs are not yet very accessible due to its high cost. The adverse events are largely unknown in neonates, but they may include hepatitis and electrolyte abnormalities.

In our study, the initial use of voriconazole achieved good clinical response: rapid presence of negative blood culture, fewer complications and almost no seriously adverse reactions. Despite the *in vitro* drug sensitivity test showed the *C. parapsilosis* was sensitive to fluconazole, some patients developed resistance to fluconazole during the clinical treatment. Because MIC interpretive breakpoints for fluconazole and *Candida spp*. from the clinical data came largely (80%) from mucosal infections and there were very few infections involving strains with elevated fluconazole MICs (28). Loss of allelic variation in the ERG11 promoter may result in a resistant strain that is homozygous for the mutated gene (29).

Voriconazole is a synthetic second-generation, broad-

spectrum triazole derivative of fluconazole. It can inhibit the cytochrome P450 (CYP)-dependent 14α-sterol demethylation in the fungi, thereby disrupting the biological synthesis of ergosterol. In Europe, intravenous and/or oral voriconazole is recommended for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients and fluconazole-resistant serious invasive *Candida spp*. infection in paediatric patients older than 2 years. Voriconazole is metabolized by hepatic CYP2C19 (the major route). The most common adverse effects of voriconazole include visual disturbance, neurologic/psychiatric disorders, hepatotoxicity, gastrointestinal effects, and skin disorders (30). In the present study, some patients developed mild to moderate liver damage, nearly no kidney damage and mild electrolyte imbalance after 3-day intravenous voriconazole treatment; only 2 patients showed temporary fundal vascular tortuosity or thinning, and all the patients were generally well tolerant. The median time to negative blood culture in the voriconazole group was also significantly shorter than in the fluconazole group; the incidence of negative blood culture after 8-day treatment was higher in the voriconazole group than in the fluconazole group; the complications and adverse effects were comparable between two groups. These findings indicate that the therapeutic effects of voriconazole are superior to those of fluconazole in the treatment of *C. parapsilosis* BSI.

In conclusion, voriconazole are safety and efficacy in the treatment of *C. parapsilosis* BSI. Our findings provide a new option for the management of invasive fungal infections and offer evidence on the clinical studies of anti-fungal treatment.

Acknowledgments

Funding: The work was funded by the Clinical Pharmacy Innovation Research Institute of Shanghai Jiao Tong University School of Medicine (2019) (No. CXYJY2019MS003).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-37

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-20-37

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-37). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Shanghai Children's Hospital (NO.: 2020R046-E01) and informed consent was taken from all the patients.

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Cite this article as: Wu Y, Wei D, Gong X, Shen Y, Zhu Y, Wang J, Gao Z. Initial use of voriconazole positively affects outcome of *Candida parapsilosis* bloodstream infection: a retrospective analysis. Transl Pediatr 2020;9(4):480-486. doi: 10.21037/tp-20-37