Pharmaceutical Care for Premature Infants with Candida Albicans Infection of the Central Nervous System

Zi-Qiang Zheng[1,2,*], Chao-Wen Yang[3] and Hong-Xia Liu[4,*]

[1]*Department of Pharmacy, The Affiliated Lianyungang Hospital of Xuzhou Medical University*

[2]*Department of Pharmacy, The First Affiliated Hospital of Kangda College of Nanjing Medical University*

[3]*Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy & School of Pharmacy, Xuzhou Medical University, Xuzhou, Jiangsu 221004, China*

[4]*Department of Pharmacy, Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China*

Abstract: *Objective:* To explore the role of clinical pharmacists in the treatment of clinical diseases by adjusting the treatment of Candida albicans infection in the central nervous system of a premature infant.

Methods: Clinical pharmacists participated in the treatment of one premature infant with Candida albicans infection of the central nervous system, and provided drug selection suggestions based on drug safety and pharmacokinetics.

Results: The doctor partially adopted the suggestions of clinical pharmacists, revised the medication plan, and the child received reasonable treatment.

Conclusion: Clinical pharmacists can make full use of pharmaceutical knowledge to serve the clinic and improve the level of rational drug use.

Keywords: Clinical phamacists, Premature infant, Central nervous system, Candida.

1. INTRODUCTION

Fungal infection of the central nervous system refers to the damage of the meninges, brain parenchyma, spinal cord or blood vessels by fungal pathogens. The annual incidence rate in developed countries is about 0.1/100,000 [1], with high mortality and poor prognosis. Therefore, it is particularly important to understand the clinical symptoms and signs of central nervous system fungal infection as early as possible, and to select appropriate therapeutic drugs for different pathogens, and even to improve the final disease results.

Central nervous system fungal infection mainly affects patients with impaired immune system, including hematological malignancies, especially acute leukemia, primary or acquired immunodeficiency, and premature infants [2-4]. PICU, trauma, autoimmune diseases or immunosuppressive agents are risk factors for fungal infection [5-10]. The routes of fungal infection in the central nervous system mainly include sinus or mastoid immersion, pulmonary infection transmission, blood source dissemination, etc [11]. Candida is a common pathogen of invasive fungal infections in the central nervous system. More than 90 % of invasive infections are caused by Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis and Candida krusei. Among them, Candida albicans has the strongest pathogenicity. In the neonatal population, invasive fungal diseases caused by Candida albicans and Candida parapsilosis are the most frequent [12], the incidence is 3-5 times higher than that of children and adults. Candida albicans is mostly caused by vertical transmission, and Candida parapsilosis can be caused by medical staff or the environment [13]. Up to 44 % of patients with candida infection are accompanied by meningitis [14, 15].

In this paper, the role of clinical pharmacists in clinical treatment was discussed according to the suggestion of drug selection provided by clinical pharmacists in the treatment of one case of neonatal central nervous system Candida albicans infection.

2. SUMMARY OF MEDICAL RECORDS

A 42-cm-tall, 1.64-kg, 1-day-old girl was admitted to the hospital on November 19, 2018 for shortness of breath after premature birth for 5 hours. The gestational age of the child was 32+1 weeks, and the birth weight was 1.63 kg. Moaning occurred immediately after birth. The hospital was treated with

*Address correspondence to this author at the Department of Pharmacy, The Affiliated Lianyungang Hospital of Xuzhou Medical University, Lianyungang, Jiangsu 222000, China;
E-mail: Zhengziqiang1216@163.com; LHX64597846@163.com

ampicillin sodium and sulbactam sodium, and then transferred to the NICU of our hospital due to low gestational age and low weight. After admission, ampicillin sulbactam was still given for anti-infection. On December 5, the patient vomited once, with milk accompanied by a small amount of light yellow liquid, and abdominal distension was obvious. PCT was 0.27 ng/ml, and cefoperazone sulbactam was replaced for anti-infection treatment. On December 9, the patient had stable body temperature, poor response, shortness of breath and milk refusal. The proportion of neutrophils was 91.1 %, CRP was higher than before. Considering the poor control of infection, meropenem was used for anti-infection treatment. On December 10, the child developed paroxysmal shortness of breath and poor response. Blood culture was unilaterally positive, and smears suggested fungi. The pathogen of infection was clear. Clinical pharmacists believed that the evidence of voriconazole for children under 2 years old was not sufficient, so fluconazole or amphotericin B was recommended. Clinicians did not adopt, plus voriconazole 6 mg/kg, ivgtt, Q12 h. On December 12, the highest temperature of the child was 37.8 °C. Cerebrospinal fluid examination confirmed central nervous system infection, WBC 33.46*10^9/L, N % 73.0 %, CRP 52 mg/L. Candida albicans was cultured in cerebrospinal fluid on December 19, and the blood concentration of voriconazole was 1.45 ng/ml on December 20. Clinical pharmacists suggested to replace it with amphotericin B liposomes, which was not considered by clinicians. On December 22, CRP showed an upward trend to 93 mg/L, and blood culture was still positive. Doctors accepted the recommendation and gave 1 mg amphotericin B, ivgtt, Qd, and gradually stopped voriconazole. On December 24, the patient responded well, the body temperature was flat, and the total number of white blood cells and CRP levels were lower than before. Therefore, voriconazole was stopped, amphotericin B was increased to 1 mg/kg, ivgtt, Qd. On December 31, the infectious index of the child did not improve significantly. Considering the poor treatment, the clinician changed to 1 mg/kg amphotericin B liposome, ivgtt, Qd. Clinical pharmacists suggested that amphotericin B liposomes should be selected and the dosage should be gradually increased to 5 mg/kg according to the weight change. Clinician adopted the suggestion and adjusted the dose on January 8 and January 10, respectively. On February 3, the child was discharged from hospital in a stable condition. During the whole process, the child's temperature was stable. Figure **1** showed the inflammatory indexes (WBC, CRP) before and after each dressing change; On the 21st day of admission, voriconazole was added for antifungal treatment, amphotericin B was used on the 31st day of admission, and amphotericin B liposome was used on the 42nd day. The use of voriconazole significantly reduced the number of white blood cells in cerebrospinal fluid, but did not alleviate the trend of increasing protein and decreasing glucose concentration in cerebrospinal fluid. When amphotericin B was replaced, the number of white blood cells in cerebrospinal fluid further decreased and the glucose concentration increased. All the indexes improved after replacing amphotericin B liposome again, as shown in Table **1**.

3. ANALYSES AND DISCUSSION

3.1. The Role of Clinical Pharmacists in the Diagnosis and Treatment of Central Nervous System Fungal Infection

This case is a premature infant with high risk factors for central nervous system fungal infection. The onset

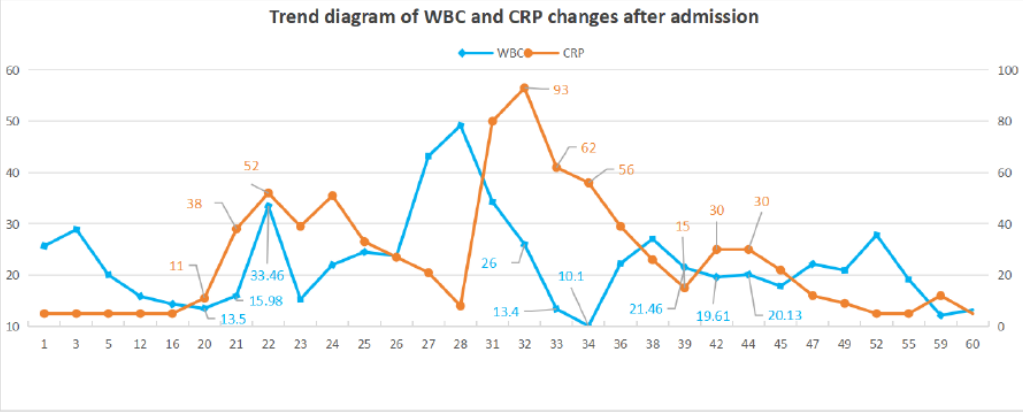

Figure 1: Trend diagram of WBC and CRP changes after admission.

Table 1: Changes of Cerebrospinal Fluid Test Indexes

Day	LDH (U/L)	Glu (mmol/L)	Protein Concentration (mg/L)	WBC (*10^6/L)
22	70	1.8	2220	1230
26	96	1	2950	26
38	51	1.5	3190	20
49	normal	1.5	2750	15

of the disease began with paroxysmal shortness of breath and poor response. Blood culture and cerebrospinal fluid specimen bacterial culture were clearly identified as Candida albicans, and the diagnosis of central nervous system fungal infection was clear. According to the 2016 IDSA Candida Clinical Practice Guidelines, amphotericin B or fluconazole is the first choice for neonatal Candida albicans infection. Amphotericin B liposome is also one of the optional drugs, which recommended dose is 3-5 mg/kg [12]. After more than ten days of voriconazole treatment, the blood culture and cerebrospinal fluid culture of the children were still positive, and the CRP level continued to rise, indicating that the treatment effect was not good. Clinical pharmacists suggested that amphotericin B liposomes should be selected and the dosage should be gradually adjusted to 5 mg/kg. The patient gradually improved and finally transferred out of NICU after the doctor chose to adopt the pharmacist's advice.

3.2. Analysis of Unsatisfactory Recovery of the Disease

Voriconazole is a broad-spectrum and highly effective triazole antifungal drug, which is a second-line treatment for Candida infection. It has better effect on Aspergillus infection and fluconazole-resistant Candida, actinomycetes and Fusarium.

Yao *et al.* [16] had shown that voriconazole was more effective in the treatment of candida meningitis than amphotericin B combined with fluconazole group and amphotericin B combined with flucytosine group, other studies had also confirmed that the efficacy and safety of voriconazole for invasive candidiasis in children aged 2-14 years were consistent with those of adults [17]. However, there was no clear evidence to prove the effectiveness of voriconazole in neonatal central nervous system infection, and IDSA guidelines did not recommend the use of voriconazole in neonates [12].

According to the Individualized Drugs for Voriconazole: Practice Guidelines for Therapeutic Drug Monitoring of the Chinese Pharmacological Society, the blood trough concentration of voriconazole should be maintained in the range of 0.5-5 mg/L[18], but the recommendation did not include newborns, especially premature infants. The trough concentration of voriconazole in this child was 1.45 mg/L, which was in line with the recommendation of the guidelines. It was suggested that the reason why neonates, especially premature infants, need to be more cautious in the use of voriconazole was the poor treatment effect, rather than the safety.

Stott *et al.* [19] summarized the concentration of different antifungal drugs in cerebrospinal fluid, found that voriconazole had a strong ability to penetrate cerebrospinal fluid, but there were significant individual differences. Studies by Irja *et al.* [20] showed that the concentration range of voriconazole in cerebrospinal fluid was 0.08-3.93 ug/mL, and the cerebrospinal fluid/plasma concentration ratio was 0.22-1.0. In addition, several researches had shown that there were large individual differences in the pharmacokinetics of voriconazole between children and adults, such as non-linear metabolism, age, weight, CYP2C19 genotype, food, liver function, drug interactions [21-24].

In order to explore the antifungal activity of voriconazole and amphotericin B against Candida albicans, Valentin *et al.* carried out *in vitro* experiments in Sabouraud's glucose broth matrix and cerebrospinal fluid, respectively. The results showed that voriconazole had only antibacterial activity against Candida albicans and no bactericidal activity. Amphotericin B had good bactericidal activity, which was significantly better than voriconazole [25]. Therefore, the author believes that these are the important reasons for the poor therapeutic effect of voriconazole in this child.

Li *et al.* [26] published a case of voriconazole combined with amphotericin B in the treatment of adult

candida meningitis, which provided a basis for amphotericin B in the treatment of candida albicans meningitis. Although Stott *et al.* [19] summarized the use of cerebrospinal fluid/plasma concentration ratio to prove that the ability of amphotericin B to penetrate cerebrospinal fluid was poor. Actually, the experimental design developed by Andreas *et al.* [27] was more convincing. They studied the distribution of four formulations of amphotericin B in cerebrospinal fluid and brain tissue in rabbit models. It was found that the distribution of different dosage forms except amphotericin B liposomes in cerebrospinal fluid was relatively uniform, and the average cerebrospinal fluid/plasma concentration ratio was about 0.23. The concentration of amphotericin B liposomes *in vivo* was significantly better than that of other dosage forms. The plasma concentration was 35-74 times that of other dosage forms, and the concentration in brain tissue was 6-10 times that of other dosage forms[27]. The extremely high blood concentration of amphotericin B liposome led to a low CSF/plasma concentration ratio. More importantly, amphotericin B and its liposomes were recommended in the IDSA guidelines for the treatment of fungal infections in children [12]. The pharmacokinetic characteristics and effectiveness of amphotericin B were comprehensively considered by clinical pharmacists with reference to relevant literature and guidelines. Finally, the child recovered well.

4. CONCLUSION

The clinical manifestations of neonatal central nervous system fungal infection are lack of specificity. Failure to diagnose in time and give reasonable and effective drug treatment may delay the condition and even lead to sequelae. During the treatment of the child, clinical pharmacists played their professional expertise and provided professional support and reasonable and effective suggestions for clinicians in the selection and use of antifungal drugs. In the whole process, clinical pharmacists play an important role and are increasingly recognized by clinicians. In the future, clinical pharmacists still need to gradually improve their ability in order to obtain a certain voice in clinical treatment, participate more in clinical treatment, and further reflect the value of clinical pharmacists.

REFERENCES

[1] Okike, I.O., *et al.*, Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004-11: an observational study. Lancet Infect Dis, 2014; 14(4): 301-7. https://doi.org/10.1016/S1473-3099(13)70332-3

[2] Hale, K.A., *et al.*, Epidemiology of paediatric invasive fungal infections and a case-control study of risk factors in acute leukaemia or post stem cell transplant. Br J Haematol, 2010; 149(2): 263-72. https://doi.org/10.1111/j.1365-2141.2009.08072.x

[3] Castagnola, E., *et al.*, Fungal infections in children with cancer: a prospective, multicenter surveillance study. Pediatr Infect Dis J, 2006; 25(7): 634-9. https://doi.org/10.1097/01.inf.0000220256.69385.2e

[4] Wattier, R.L., *et al.*, A Prospective, International Cohort Study of Invasive Mold Infections in Children. J Pediatric Infect Dis Soc, 2015; 4(4): 313-22. https://doi.org/10.1093/jpids/piu074

[5] Jaworski, R., *et al.*, Fungal infections in children in the early postoperative period after cardiac surgery for congenital heart disease: a single-centre experience. Interact Cardiovasc Thorac Surg, 2016; 23(3): 431-7. https://doi.org/10.1093/icvts/ivw156

[6] Klingspor, L., *et al.*, Invasive Candida infections in surgical patients in intensive care units: a prospective, multicentre survey initiated by the European Confederation of Medical Mycology (ECMM) (2006-2008). Clin Microbiol Infect, 2015; 21(1): 87 e1-87 e10. https://doi.org/10.1016/j.cmi.2014.08.011

[7] Tragiannidis, A., *et al.*, Invasive fungal infections in pediatric patients treated with tumor necrosis alpha (TNF-alpha) inhibitors. Mycoses, 2017; 60(4): 222-229. https://doi.org/10.1111/myc.12576

[8] Silva, M.F., *et al.*, A Multicenter Study of Invasive Fungal Infections in Patients with Childhood-onset Systemic Lupus Erythematosus. J Rheumatol, 2015; 42(12): 2296-303. https://doi.org/10.3899/jrheum.150142

[9] Jordan, I., *et al.*, Per-species risk factors and predictors of invasive Candida infections in patients admitted to pediatric intensive care units: development of ERICAP scoring systems. Pediatr Infect Dis J, 2014; 33(8): e187-93. https://doi.org/10.1097/INF.0000000000000274

[10] de Araujo Motta, F., *et al.*, Risk Adjustment for Congenital Heart Surgery Score as a Risk Factor for Candidemia in Children Undergoing Congenital Heart Defect Surgery. Pediatr Infect Dis J, 2016; 35(11): 1194-1198. https://doi.org/10.1097/INF.0000000000001277

[11] Schwartz, S., *et al.*, Advances in the diagnosis and treatment of fungal infections of the CNS. Lancet Neurol, 2018; 17(4): 362-372. https://doi.org/10.1016/S1474-4422(18)30030-9

[12] Pappas, P.G., *et al.*, Executive Summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis, 2016; 62(4): 409-17. https://doi.org/10.1093/cid/civ1194

[13] Calley, J.L. and A. Warris, Recognition and diagnosis of invasive fungal infections in neonates. J Infect, 2017; 74 Suppl 1: S108-S113. https://doi.org/10.1016/S0163-4453(17)30200-1

[14] Faix, R.G., Systemic Candida infections in infants in intensive care nurseries: high incidence of central nervous system involvement. J Pediatr, 1984; 105(4): 616-22. https://doi.org/10.1016/S0022-3476(84)80433-3

[15] Baley, J.E. and R.A. Silverman, Systemic candidiasis: cutaneous manifestations in low birth weight infants. Pediatrics, 1988; 82(2): 211-5. https://doi.org/10.1542/peds.82.2.211

[16] Yao, Y., *et al.*, Voriconazole: a novel treatment option for cryptococcal meningitis. Infect Dis (Lond), 2015; 47(10): 694-700. https://doi.org/10.3109/23744235.2015.1044260

[17] Martin, J.M., *et al.*, Safety, Efficacy, and Exposure-Response of Voriconazole in Pediatric Patients With Invasive Aspergillosis, Invasive Candidiasis or Esophageal Candidiasis. Pediatr Infect Dis J, 2017; 36(1): e1-e13. https://doi.org/10.1097/INF.0000000000001339

[18] Chen, K., *et al.*, Individualized Medication of Voriconazole: A Practice Guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Ther Drug Monit, 2018; 40(6): 663-674. https://doi.org/10.1097/FTD.0000000000000561

[19] Stott, K.E. and W. Hope, Pharmacokinetics-pharmacodynamics of antifungal agents in the central nervous system. Expert Opin Drug Metab Toxicol, 2018; 14(8): 803-815. https://doi.org/10.1080/17425255.2018.1492551

[20] Lutsar, I., S. Roffey, and P. Troke, Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis, 2003; 37(5): 728-32. https://doi.org/10.1086/377131

[21] Bartelink, I.H., *et al.*, Highly variable plasma concentrations of voriconazole in pediatric hematopoietic stem cell transplantation patients. Antimicrob Agents Chemother, 2013; 57(1): 235-40. https://doi.org/10.1128/AAC.01540-12

[22] Yamada, T., *et al.*, Saturated Metabolism of Voriconazole N-Oxidation Resulting in Nonlinearity of Pharmacokinetics of Voriconazole at Clinical Doses. Biol Pharm Bull, 2015; 38(10): 1496-503. https://doi.org/10.1248/bpb.b15-00241

[23] Michael, C., *et al.*, Voriconazole pharmacokinetics and safety in immunocompromised children compared to adult patients. Antimicrob Agents Chemother, 2010; 54(8): 3225-32. https://doi.org/10.1128/AAC.01731-09

[24] Spriet, I., *et al.*, Voriconazole plasma levels in children are highly variable. Eur J Clin Microbiol Infect Dis, 2011; 30(2): 283-7. https://doi.org/10.1007/s10096-010-1079-8

[25] Al Jalali, V., *et al.*, In vitro activity of voriconazole and amphotericin B against Candida albicans, Candida krusei, and Cryptococcus neoformans in human cerebrospinal fluid. Infection, 2019; 47(4): 565-570. https://doi.org/10.1007/s15010-019-01275-9

[26] Li, S.S., *et al.*, Voriconazole combined with low-dose amphotericin B liposome for treatment of cryptococcal meningitis. Infect Dis (Lond), 2016; 48(7): 563-5. https://doi.org/10.3109/23744235.2016.1157897

[27] Groll, A.H., *et al.*, Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental Candida albicans infection of the central nervous system. J Infect Dis, 2000; 182(1): 274-82. https://doi.org/10.1086/315643

Received on 24-10-2023 Accepted on 29-11-2023 Published on 05-12-2023

DOI: https://doi.org/10.12974/2311-8687.2023.11.15