



Major article

Integrated measures for prevention of invasive *Candida* infections in preterm infants in a Chinese neonatal intensive care unit



Jiahui Chen MS^a, Xiaodan Yu MD, PhD^b, Yijun Zhou MS^a, Yongjun Zhang MD, PhD^a, Jianxing Zhu MD^a, Lijuan Xie MD, PhD^a, Jihong Qian MD, PhD^a, Qingnan Yang MD^a, Hongping Xia MD, PhD^a, Tianwen Zhu MD, PhD^a, Yonghong Zhang MD, PhD^a, Yan Chen MD, PhD^a, Dongying Zhao MD, PhD^a, Zhenjuan He MD, PhD^{a,c,*}

^a Neonatology Department, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

^b MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

^c Shanghai Institute for Pediatric Research, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

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Background: The increasing incidence of invasive *Candida* infections (ICIs) in preterm infants in the neonatal intensive care unit (NICU) of Xinhua Hospital aroused our concern. We undertook a retrospective study to evaluate the efficacy of different preventive measures for ICI in preterm infants.

Methods: Preterm infants with gestational age (GA) <33 weeks admitted between 2010 and 2013 were divided into 3 groups according to the preventive measures applied in different periods: the control group (CG), fluconazole group (FG), and integrated measures group (IMG). We analyzed the incidence of ICI and distribution of fungal pathogens in these 3 groups, and also evaluated the efficiency of various measures in preventing ICIs in preterm infants.

Results: The study sample comprised 261 preterm infants born at <33 weeks GA, including 94 in the CG, 99 in the FG, and 68 in the IMG. The differences among the groups were not significant at baseline. ICI developed in 41 of the 261 infants (15.7%). The incidence of ICI varied significantly among the groups: 22.3% in the CG (21/94), 18.2% in the FG (18/99), and only 2.9% in the IMG (2/68) ($P = .003$). ICI was less frequent in the IMG compared with the CG ($P < .001$) and the FG ($P = .003$).

Conclusions: The integrated measures approach is meaningful for the prevention of ICIs in preterm infants in NICUs with many patients but inadequate medical resources in some developing countries.

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The development of perinatal medicine and neonatal care has allowed more preterm infants to survive with lower gestational age (GA) and birth weight (BW) in developing countries. Meanwhile, invasive *Candida* infection (ICI) is increasingly common in neonatal intensive care units (NICUs). Fungi, especially *Candida* species, are currently the third most frequent causal agent of late-onset sepsis in preterm infants, with an estimated incidence of 2.6%–16.7% in very low birth weight infants ($\leq 1,500$ g) and of 5.5%–20% among extremely low birth weight infants ($\leq 1,000$ g) in NICUs, and a crude mortality rate hovering around 30%.¹⁻¹⁰

* Address correspondence to Zhenjuan He, MD, PhD, Neonatology Department, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Rd, Shanghai 200092, China.

E-mail address: hezhenjuan@sjtu.edu.cn (Z. He).

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The most common causative pathogen of invasive fungal infections (IFIs) in preterm infants is *Candida* spp, with *Candida albicans* the most common species. *Candida parapsilosis* is the second most common pathogen and occasionally has been reported as the predominant species in the last decade.¹¹⁻¹⁴ Diagnosis may be delayed because of a nonspecific clinical presentation; difficulty in culturing the organisms from blood, cerebrospinal fluid, or urine; and the need to await culture results. Treatment can involve a long and costly therapeutic course. Furthermore, IFI in preterm infants carries a high mortality and leads to significant neurodevelopment impairment in survivors.¹⁴⁻¹⁶ Thus, effective prevention of IFI in preterm infants is of vital importance.

Starting in early 2010, an increasing number of nosocomial ICIs in our NICU began to draw the attention of the medical staff. Published studies demonstrated the efficacy and safety of fluconazole prophylaxis in preterm infants with no significant adverse

effects reported,^{3-6,10,11} and we took the experience of these studies for reference. In July 2011, we began to give intravenous prophylactic fluconazole to all preterm infants of <33 weeks GA in our NICU, in addition to the routine measures for nosocomial infection prevention. Disappointingly, however, the high rate of ICIs in preterm infants in our NICU persisted, and so we continued to seek a solution.

It has long been recognized that handwashing is an effective and inexpensive means of preventing nosocomial infections, especially when handwashing compliance is sustained over long periods.^{17,18} In December 2012, we began to strengthen the management and supervision of hand hygiene, along with continuing the routine preventive measures and fluconazole prophylaxis. We found an obvious reduction of the number of ICI cases. The goal of the present study was to examine the efficacy of different measures in preventing ICI in preterm infants of <33 weeks GA in the NICU.

METHODS

This retrospective study was conducted at the NICU of Xinhua Hospital, Shanghai, China, a level III unit with 50 beds. The study was approved by the hospital's Institutional Review Board. Preterm infants of <33 weeks GA and ≤ 7 days of age admitted to our NICU between 2010 and 2013 were eligible for enrollment. The exclusion criteria were survival for <7 days, presence of ICI within the first 3 days of life, and incomplete data or charts.

The study infants were grouped into 3 cohorts based on the preventive measure applied. The control group (CG) comprised infants admitted between January 1, 2010, and June 30, 2011. In this group, only routine measures for prevention of nosocomial infections were applied, including disinfection and sterilization, isolation of patients, control of risk factors, and education and training of medical staff. The fluconazole group (FG) comprised infants admitted between July 1, 2011, and November 30, 2012. In addition to routine preventive measures, all eligible infants received prophylactic intravenous fluconazole beginning on day of life 7. The dosing regimen was 5 mg/kg fluconazole (Diflucan; Pfizer Italia, Rome, Italy) every other day for 3 weeks or until earlier discharge, death, or the onset of ICI.

The integrated measures group (IMG) comprised infants admitted between December 1, 2012, and December 31, 2013. During this period, routine preventive measures and fluconazole prophylaxis were administered, and also the management and supervision of hand hygiene was emphasized. Every medical worker was required to wash his or her hands with running water and hand sanitizer (Avagard 9230M; 3M Health Care, Shanghai, China), a cleanser without chlorhexidine gluconate, povidone-iodine, or ethyl alcohol, instead of only a waterless hand sanitizer (Avagard 9250P; 3M Health Care), a solution containing 0.45%~0.55% chlorhexidine gluconate and 63.1%~77.0% ethyl alcohol, before and after touching an infant or performing a procedure. The correct steps for handwashing were posted on the wall above each sink, where they could be readily seen by all staff. Monthly training lectures on the importance of hand hygiene and the correct steps of handwashing were provided to staff working in the NICU. The doctors and nurses were observed and supervised by one another and by chief physicians and head nurses anytime and anywhere in the NICU.

Through the hospital's electronic medical records system, data were collected on each infant's GA, BW, sex, and Apgar scores; duration of endotracheal intubation; use of a peripherally inserted central catheter, gastric tube, or total parenteral nutrition; use of cephalosporin or carbapenem antibiotics; late-onset bacterial sepsis (positive blood culture after 3 days of life); necrotizing enterocolitis; and length of NICU stay; and maternal characteristics,

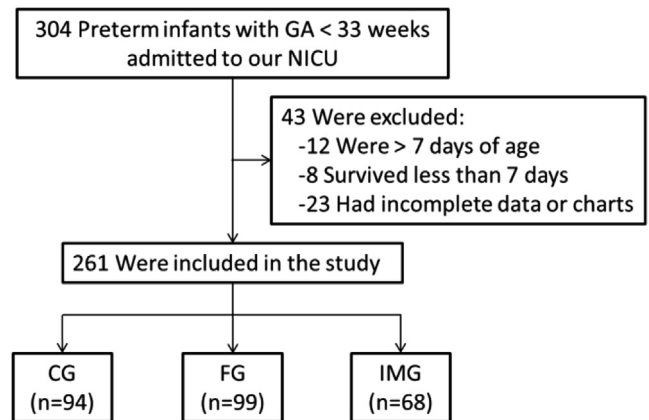


Fig. 1. Flowchart of the study participants.

including age, delivery mode, multiple gestation, presence of pre-eclampsia, presence of premature rupture of membranes, and use of antenatal antibiotics and steroids.

According to the international consensus documents promulgated by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group¹⁹ and the guidelines published by the Society of Critical Care Medicine, Chinese Medical Association,²⁰ the diagnostic criterion for ICI is a positive culture result of fungi from blood, urine, or cerebrospinal fluid with clinical signs of neonatal sepsis.

Statistical analysis

All statistical analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL). Continuous variables were analyzed using the Student *t* test and analysis of variance, as appropriate. Categorical variables were analyzed using the χ^2 and Fisher's exact tests, as appropriate. Nonparametric comparisons among the 3 groups were made using the Kruskal-Wallis test.

RESULTS

Study participants

A total of 304 preterm infants of <33 weeks GA were admitted to our NICU during the study period (Fig 1). Forty-three of these preterm infants were excluded, including 12 who were age >7 days on admission, 8 who survived <7 days after birth, and 23 who had incomplete data or charts. The excluded patients did not differ from the included patients in terms of GA or BW. The final study sample comprised 261 preterm infants of <33 weeks GA, including 94 in the CG, 99 in the FG, and 68 in the IMG.

Table 1 present demographic and clinical characteristics and risk factors for ICI for the 3 study groups. The differences at baseline were not significant among the groups.

IFI

ICI developed in 41 of the 261 (15.7%) preterm infants of <33 weeks GA during the study period. The mean GA was 30.51 ± 1.46 weeks (range, 27.86-32.86 weeks), and the mean BW was $1,382.44 \pm 341.35$ g (range, 900-2,800 g). Among the 41 infants with ICI, 37 (90.2%) had a positive fungal culture within the first 28 days of life. The mean age at the first episode of ICI was 18.73 ± 7.63 days (range, 5-43 days). All 41 ICI cases had positive culture results of

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