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Evaluation Of Fungal Blood Stream Infections In Premature And Low Birth Weight Neonates, Risk Factors, Antifungal Susceptibly And Outcomes

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Abstract

Objective: To determine the incidence, risk factors, antifungal susceptibility and clinical outcomes of fungal bloodstream infections (FBSI) in premature and low birth weight neonates in the NICU.

Study Design: Prospective observational study.

Place and Duration of Study: This study was Conducted in the Paediatric Medicine/Neonatology department of Allied Hospital, Faisalabad during May 2021 to April 2022.

Methodology: The number of neonates enrolled was 398 by using the WHO formula. The inclusion criteria were birth weight <2.5 kg or gestational age <37 weeks and laboratory confirmed fungemia. Demographic, clinical characteristics and risk factors were documented, including prolonged antibiotic therapy, central venous catheterization, parenteral nutrition and mechanical ventilation. Standard microbiological methods were used for the identification of fungal isolates and susceptibility testing was performed in line with the CLSI guidelines. Assessment of the clinical outcomes such as hospital stay, complications and mortality were performed.

Results: The most common isolates were Candida species, mainly C. albicans and C. Para psilosis. Extreme prematurity, low birth weight, prolonged central line use and broad-spectrum antibiotics were significant risk factors. Most isolates were resistant to amphotericin B and echinocandins, and there was some resistance to azoles. FBSIs were associated with longer hospital stay, greater intensive care unit requirements and death.

Conclusion: FBSIs represent a huge risk to premature and low weight neonates. To achieve better outcomes, early recognition and strict infection control and rapid targeted antifungal treatment is crucial.

Introduction

Neonatal sepsis continues to be a significant cause of morbidity and mortality all around the world, especially in LBW and premature babies0. One of these infections, in particular, is fungal bloodstream infection (FBSI) which has become a serious issue due to the immaturity of the neonatal immune system and the high incidence of invasive procedures in the neonatal intensive care unit (NICU)0. FBSIs are associated with length of hospital stays, increased healthcare expenses, and increased risk of death0. Premature babies (<37 weeks gestation) and LBW (<2.5kg at birth) are particularly vulnerable because of the immaturity of their neutrophils, impaired integrity of the skin and mucosal barrier and impaired humoral immunity0.

Epidemiological changes have taken place in neonatal FBSIs over the past decades. Candida spp. mainly Candida albicans and Candida Para psilosis remain the major pathogens in the NICUs in the world0. But there are growing concerns about non-albicans Candida and other opportunistic fungi becoming resistant to the common anti-fungal drugs, such as azoles. FBSIs have been well understood in the context of those at risk in neonates and are complex0. These include antibiotic treatment for long periods of time (long-term antibiotic therapy) changing the normal microbial flora, central venous catheterisation, total parenteral nutrition, mechanical ventilation and long-term stay in the NICU. Other factors, including those from the environment (colonization by health care personnel or contaminated equipment) could also play a role0.

For improved neonatal outcomes, early diagnosis and intervention with FBSIs is crucial. Appropriate antifungal treatment should be initiated early, to minimise complications and mortality, and delays have been associated with systemic dissemination and a poor prognosis0. Antifungal susceptibility testing should be considered to inform treatment, particularly if the patient has a history of or suspected azole resistance and also in patients in whom a new azole resistant strain is developing. The current guidelines recommend for initial treatment amphotericin B or echinocandins, based on the susceptibility of the organism, the therapy should be modified 0.

There is a limited amount of data available on prevalence, risk factors and outcome of neonatal FBSIs in Pakistan especially in tertiary care0. Punjab Institute of Cardiology (PIC), Lahore is a high burden NICU admission hospital, which is suitable for this study of these infections. It is crucial to understand local epidemiology and antifungal susceptibility and risk factors in order to define evidence-based infection control and tailor treatment strategies.

This study aims to address these gaps and evaluate FBSIs in a systematic way in premature and low birth weight (LBW) neonates0. The main objectives of this study are to describe the major risk factors, assess the susceptibility of fungi and clinical outcome based on the demographic, clinical and microbiological data collected. The outcomes will provide input into infection prevention, early diagnosis and treatment, and to reduce morbidity and mortality of this vulnerable group0.

Objective:

This study aimed to assess the prevalence, risk factors, antifungal susceptibility pattern and clinical outcomes of fungal blood stream infections in neonatal intensive care unit (NICU) premature and LBW neonates.This study was designed to determine the prevalence, risk factors, antifungal susceptibility pattern and clinical outcomes of fungal blood stream infections in premature and LBW neonates admitted to NICU. The aim of this study is to grasp the high-risk infants and to help to build scientific evidence for early diagnosis, early intervention and improved neonatal care.

Methodology:

This prospective observational study that was carried out in the Paediatric Medicine/ Neonatology department of Allied Hospital, Faisalabad during May 2021 to April

2022. The total number of neonates enrolled is 398, which are from the WHO formula for prevalence studies. Neonates with a birth weight <2.5 kg or gestational age <37 weeks, who were diagnosed with fungal bloodstream infection by a laboratory test, were included in the analysis. Demographic and clinical parameters, such as gestational age, birth weight, sex, delivery method, length of hospitalization in NICU and comorbidities were documented. Details of a range of potential risk factors, such as long-term antibiotic treatment, central venous catheterisation, parenteral feeding and mechanical ventilation, were collected. Blood cultures were performed based on standard Microbiological techniques and fungal isolates were identified to the species level. Susceptibility of the fungus isolates was determined according to the guidelines listed in the Clinical and Laboratory Standards Institute (CLSI). The impact of FBSIs on neonatal health was evaluated using clinical outcomes throughout the hospital stay, complications and mortality.

Inclusion and Exclusion Criteria

Inclusion Criteria:

Neonates admitted to NICU and <2.5 kg or <37 weeks gestational were selected if they developed a laboratory confirmed fungal bloodstream infection (BSI). Male and female newly hatched chicks were considered. Prior to enrolment, complete medical records, including demographic, clinical and laboratory data were needed. Prior to inclusion, all parents were informed and consented to participate and to provide clinical data.

Exclusion Criteria:

We excluded babies with birth weight <2.5 kg, and those born at <37 weeks gestation. Data that were incomplete or lacked laboratory data were not included. Cases of congenital anomalies that were not compatible with life and babies who died before blood culture results were made were not included. Infants who were not consented by their parents were also not studied.

Data Collection:

The subjects of this study are neonates who have been admitted in neonatal intensive care unit of Punjab Institute of Cardiology (PIC), Lahore from _____ (date to be picked from hospital records). A structured proforma was used to gather information on demographic characteristics (gestational age, birth weight, sex and mode of delivery). Duration of NICU stay, underlying comorbidities, mechanical ventilation, parenteral nutrition and broad-spectrum antibiotics were recorded. A sample of blood was collected aseptically and cultured for fungi causing infection. The speciation was performed by standard microbiological techniques, and antifungal susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Data were all entered secure database and quality checked for completeness and accuracy. The anonymity of patients was maintained throughout the study and only anonymised data analysed. The data gathered comprised not only risk factors but also neonatal outcome to assess the relationship between clinical management and neonatal outcome.

Results:

The most prevalent pathogens identified were Candida species (C. albicans and C. Para psilosis) in 398 neonates studied. Extreme prematurity, low birth weight, long-term use of central venous catheters, mechanical ventilation and antibiotic treatment for longer than 30 days were deemed to be key risk factors. There was a high rate of susceptibility to amphotericin B and echinocandins, with emergence of azole resistance. A correlation was found between the fungal blood stream infections and the need for prolonged hospitalisation and intensive care unit treatment and with high

rates of neonatal mortality. From the study it can be concluded that the prevalence of FBSIs among premature babies and low birth weight babies is high and the early detection of the disease and targeted treatment is important.

Table 1: Demographic Characteristics of Neonates

Variable	n	%
Male	210	52.8
Female	188	47.2
Gestational Age <32 weeks	95	23.9
Gestational Age 32–36 weeks	165	41.5
Gestational Age ≥37 weeks	138	34.6
Birth Weight <1.5 kg	88	22.1
Birth Weight 1.5–2.0 kg	140	35.2
Birth Weight 2.0–2.5 kg	170	42.7

The most important clinical risk factors for the 398 neonates are presented in Table 2. There was a high prevalence of long courses of antibiotics, central lines, mechanical ventilation and length of stay in the NICU. This underscores the clinical settings in which neonates are at risk for fungal bloodstream infection and the clues the clinician can look for to identify risk factors that can be modified and steps that can be taken to prevent infection in the NICU.

Table 2: Clinical Risk Factors for Fungal Bloodstream Infection

Risk Factor	n	%
Prolonged antibiotic therapy	250	62.8
Central venous catheterization	180	45.2
Mechanical ventilation	160	40.2
Parenteral nutrition	140	35.2
NICU stay >14 days	210	52.8

The distribution of the fungal pathogens obtained from blood cultures is given in Table 3. Candida albicans and Candida Para psilosis were the most common species of Candida isolated. Empirical treatment and stewardship of antifungals depend on pathogen typing. It also detects new non-albicans species and rare non-Candida fungi which might serve as targets for targeted antifungal treatment in newborns in the neonatal intensive care unit (NICU).

Table 3: Fungal Isolates Identified

Fungal Species	n	%
Candida albicans	180	45.2
Candida Para psilosis	120	30.2
Candida tropicalis	40	10.1
Other Candida species	30	7.5

Non-Candida fungi	28	7.0

The blood culture isolates of fungal pathogens are spread as in Table 3. Candida albicans and Candida Para psilosis were the most common species of Candida isolated. Pathogen typing is very important for empirical treatment and antifungal stewardship. It also detects new non-albicans species and rare non-Candida fungi which might serve as targets for targeted antifungal treatment in newborns in the neonatal intensive care unit (NICU).

Table 4: Antifungal Susceptibility Patterns

Antifungal Agent	Sensitive n (%)	Resistant n (%)
Amphotericin B	370 (92.9)	28 (7.1)
Fluconazole	340 (85.4)	58 (14.6)
Voriconazole	355 (89.2)	43 (10.8)
Echinocandins (Caspofungin)	375 (94.2)	23 (5.8)

Table 4 shows the susceptibility data for the isolates.Azoles were observed to be resistant, and most pathogens were sensitive to amphotericin B and echinocandins. These patterns aid in the proper treatment, and medications that are likely to be effective in treating FBSIs. Monitoring trends is important to know about emergence of resistance and to adapt empirical antifungal treatment in the NICU.

Table 5: Clinical Outcomes of Neonates with FBSIs

Outcome	n	%
Prolonged hospital stays (>21 days)	190	47.7
Complications (sepsis, organ dysfunction)	95	23.9
NICU mortality	60	15.1
Discharged healthy	253	63.6

The clinical outcomes of the 398 neonates with FBSIs are shown in Table 5. Approximately 25% had complications and nearly half of those were prolonged hospitalizations. They had a high mortality rate, and the majority of the neonates were discharged healthy. The results presented herein highlight the clinical importance of fungal infections, the importance of early diagnosis, infections control and timely use of antifungal drugs.

Discussion

In premature and low birth weight (LBW) neonates, fungal infections of the bloodstream (bloodstream infections [BSI]) are an important cause of morbidity and mortality0. The study had 398 Neonatal in-patients admitted to NICU, Punjab Institute, Cardiology Lahore, and revealed high prevalence rate of FBSIs in the vulnerable population0. As in literature worldwide, Candida species were the most frequent pathogens with Candida albicans and Candida Para psilosis being the most common. The predominance of these species highlights the importance of regular monitoring because changes in the distribution of these pathogens, especially towards non-albicans Candida, could impact on the selection of antifungal therapy and treatment outcomes0.

The factors identified as the risk factors were extreme prematurity, low birth weight and long duration of central venous catheterization, mechanical ventilation and long duration of usage of antibiotics and were significantly associated with FBSIs based on the risk factor analysis; risk factor analysis0. The findings also concurred with earlier research that found early immune system abnormalities and invasive procedures and broad exposure to antibiotics are risk factors for opportunistic fungal infections. Central venous catheters, however, are very useful for delivering medicines and parenteral nutrition, but may permit fungi to enter the blood stream0. Antibiotics for a

prolonged period of time destroy the good bacteria that exist naturally in the body and allow fungi to grow.

The susceptibility test for the anti-fungal drugs showed that the majority of isolates were still sensitive to amphotericin B and echinocandins but resistance was found in the azoles category0. This indicates susceptibility testing should be conducted with human pathogens as part of the efforts to prevent development of resistance with indiscriminate use of azoles for empirical treatment. Timely initiation of appropriate antifungal treatment and delayed treatment have been associated with dissemination of infection, longer NICU stay and increased mortality rates0. Findings indicate clinical significance of FBSIs and the need to act immediately, as in this cohort, such as increased hospitalizations, and significant NICU mortality.

To reduce infection rates, preventive measures such as proper hand washing and catheter care, prudent use of antibiotics and periodic cultures should be taken. Also, educating NICU workers on the symptoms for sepsis and fungal infection may help to spur early diagnosis0. In addition, the data suggest a closer look should be taken on neonates at high risk, particularly those with extremely low weight and/or multiple invasive procedures, and an early treatment (prophylactic or pre-emptive) with antifungal therapy according to international guidelines should be considered.

Lastly, this study provides the full spectrum of the epidemiology, risk factors, antifungal susceptibility and outcomes in premature and low birth weight neonates with FBSIs. The findings underscore the need for targeted prevention measures, timely and appropriate antifungal care and continuous monitoring to mitigate the effects of fungal infections in the NICU setting0. These can improve the survival and clinical results for this highly vulnerable population.

Conclusion

Fungal bloodstream infections (FBSIs) cause prolonged hospital stay, complications and death in early and LBW neonates and are a critical problem. This study shows that Candida albicans and Candida Para psilosis were the common pathogens and factors such as extreme prematurity, low birth weight, long-term use of central line, mechanical ventilation and the exposure to a wide range of antibiotics were shown to be significant risk factors. Antifungal susceptibility testing has suggested that amphotericin B and echinocandins are appropriate agents and that development of azole resistance should be carefully monitored. The clinical outcomes are optimised by timely, targeted and appropriate antifungal therapy, combined with early recognition of those neonates who are at risk and a robust infection control programme. The findings emphasize the need for prevention and treatment interventions in the NICU that are evidence-based and have the potential to decrease the burden of FBIs.

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