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A Study of Predisposing factors for Fungal Sepsis and Causative Organisms

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Abstract **Original Research Article**

Neonatal sepsis is the most common cause of neonatal mortality and morbidity. Studies have recorded an incidence of neonatal sepsis, varying between 11 and 24.5 per 1000 live births. It is responsible for about 30-50% of the neonatal deaths. Depending on the onset of symptoms, it can be classified into early onset sepsis within 72 h of life and late onset sepsis usually after 72 h of life. It has been one of the major diagnostic problems for physicians due to non-specific symptoms and the absence of a reliable Para clinical marker. Fungal blood stream infection (BSI) is an important cause of neonatal sepsis and sepsis related mortality. According to our study, the common risk factors for Fungal BSI include prematurity, low birth weight, central vascular catheterization, use of broad spectrum antibiotics, prolonged hospital stay, birth canal infections or discharges and male newborns. Neonatal fungal sepsis occurs in immunologically immature or very ill patients because of individual susceptibility and due to health care related infection. Early signs of sepsis are non-specific and may commonly presents with respiratory distress, feed refusal, apnoea and bulging fontanelle etc. A heart rate above 160 can also be an indicator of sepsis, this tachycardia can present even 24 hours before the onset of other signs. Culturing for microorganisms from a sample of CSF, blood or urine, is the gold standard test for definitive diagnosis of neonatal sepsis. Widespread infection despite negative culture is common. It is often difficult to establish the diagnosis of fungal sepsis because there are no easy, reliable and rapid tests. In addition to fluid resuscitation and supportive care, Amphotericin B continues to be the mainstay of therapy for systemic fungal infections. Recently Indian liposomal Amphotericin B derived from neutral lipids (L-Amp-LRC-1) has shown effective response at lower dose with less toxicity and inexpensive drug for the treatment of neonatal candidiasis.

Keywords: Neonatal sepsis, fungal blood stream infections, Neonatal mortality, prematurity, low birth weight.

INTRODUCTION

Neonatal sepsis is defined as a disseminated disease with positive blood culture during the first month of life, and encompasses various systemic infections of the newborn. It is more common in developing countries compared to developed countries. Neonatal sepsis is the most common cause of neonatal mortality and morbidity. Studies have recorded an incidence of neonatal sepsis, varying between 11 and 24.5 per 1000 live births. It is responsible for about 30-50% of the neonatal deaths [1]. Depending on the onset of symptoms, it can be classified into early onset sepsis within 72 h of life and late onset sepsis usually after 72 h of life. Knowledge about potential risk factors would help in the early diagnosis of sepsis. Early signs of sepsis are non-specific and subtle. It has been one of the major diagnostic problems for physicians due to non-specific symptoms and the absence of a reliable Para clinical marker [2]. Advances in neonatal management have led to considerable improvement in newborn survival. However, early (<72 hours) and late (>72 hours) onset systemic infections, both bacterial and fungal remain a devastating complication and an important cause of morbidity in these babies [3].

Fungal blood stream infection (BSI) is an important cause of neonatal sepsis and sepsis related mortality. Neonatal fungal sepsis occurs in immunologically immature or very ill patients because of individual susceptibility and of health care related infections. Candida species are the most frequently isolated agents (93% to 99%) [4]. Candida has emerged to be one of the most common causes of neonatal fungemia and the third most common overall cause of neonatal late onset sepsis in infants whose birth weight is less than 1500g. Candida accounts for up to 13% of such infections with most of the surveillance studies

reporting a rising trend. Until recently, Candida albicans was by far the predominant species in most countries, responsible for 60% of all cases of candidemia. However, recently several countries around the world have witnessed a change in the epidemiology of Candida infections, characterized by a progressive shift from a predominance of C. albicans to non-albicans Candida species notably C. tropicalis, C. parapsilosis, C. krusei, C. guilliermondii and C. glabrata [5]. Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis is difficult. Signs of fungal sepsis include thrombocytopenia, lethargy, glucose instability, increasing ventilation requirement and apnoea. The objective of this study is to identify the risk factors and fungal infections (isolate and identify causative organism) causing Neonatal Septicemia.

AIM AND OBJECTIVES

To study the risk factors for fungal sepsis in newborns and to identify fungal species.

METHODS

Table-01: Neonatal and Maternal risk factors associated with Neonatal Sepsis

VARIABLES		NO OF CASES OF FUNGAL SEPTICEMIA	TOTAL NO OF CASES OF NEONATAL SEPTICEMIA	PERCENTAGE (%) OF CASES OF FUNGAL SEPTICEMIA
NEONATAL RISK FACTORS	>2 Broad Spectrum Antibiotic use	5	79	4.5
	Prolonged Hospital Stay	5	55	4.5
	Nil Orally >5 days	5	44	4.5
	Central Line Insert	5	66	4.5
	Mechanical Ventilation	1	18	0.9
	Use of H_2 Antagonist	3	14	2.7
PRENATAL RISK FACTORS	Pregnancy induced hypertension	1	4	0.9
	Bleeding	1	9	0.9
	Antenatal Steroids	3	38	2.7
	History of Fever	4	58	3.6
	Foul Smell Discharge	3	19	2.7
	Leaking Per Vaginal	5	53	4.5
NEONATAL SEX	MALE		65	
	FEMALE		45	
BIRTH WEIGHT (Kg)	<1.0Kg	0	2	0.0
	1.0-1.5 Kg	0	35	0.0
	1.6-2.5 Kg	3	51	2.7
	>2.5Kg	1	22	0.9
GESTATIONAL AGE (Weeks)	≤32 weeks	2	42	1.8
	33-36 weeks	2	29	1.8
	>37 weeks	1	39	0.9
PARITY	Primi	5	75	4.5
	Multi	1	35	0.9

This study is a hospital based prospective observational study, conducted during October 2017 to December 2018 in Department of Paediatric Medicine, SMS Medical College and attached group of hospitals, Jaipur. Neonates from birth to 28 days of life who were suspected neonatal septicemia were enrolled in the study. A sample size of 110 cases was covered. Detailed history and physical examination was done for all the patients. Blood samples from cases of neonatal septicemia were taken. The samples were processed in the Department of Microbiology to identify causative organism of suspected infection. For blood culture, Brain Heart Infusion (BHI) broth in 1:10 dilution were inoculated and incubated at 37^{o}C for 48 hrs. Any growth observed was subcultured on Blood Agar, Mckonkey's Agar and Sabroud's Dextrose Agar (SDA) with Chloramphenicol (0.05%). Species of fungal infection were identified by Colony Morphology on SDA, Color on Chromogenic Media, Growth at 45^{o}C, Germ Tube test, Chlamydospore formation and Carbohydrate Fermentation. Neonates other than blood stream infection, seropositive mothers and refusal to give consent were not included in the study.

RESULT

Interpretation

1. Use of > 2 broad spectrum antibiotics, central line insertion and prolonged hospital stays are the most common neonatal risk factors accounting neonatal sepsis.

2. Birth canal infections with discharges and/or fever are the most prenatal risk factors accounting neonatal sepsis.
3. Male newborns are more prone for neonatal infections than female newborns.
4. Low birth weight and premature infants are more prone for neonatal sepsis.

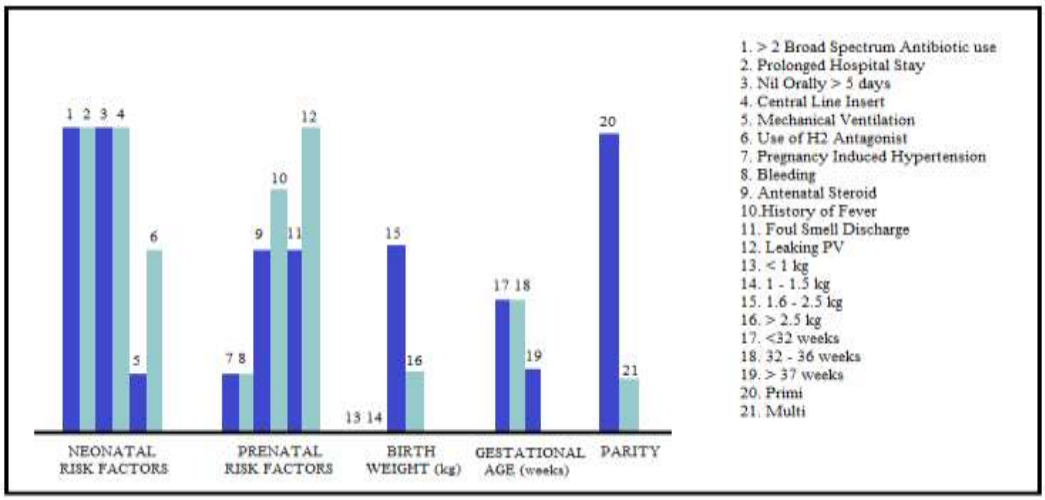

Fig-01: Neonatal and Maternal risk factors associated with Neonatal Sepsis

Table-02: Clinical signs and symptoms observed in septicemic neonates

Clinical Signs and Symptoms of septicemic neonates	Number of cases	Percentage (%)
Cyanosis	4	3.6
Edema	11	10
Perinatal Asphyxia	23	20.9
Respiratory Distress	60	54.5
Refusal to Feed	97	88.1
Apnoea	65	59.1
Neonatal convulsion	17	15.4
Oliguria	17	15.4
Hypothermia (< 35.4 ^{o}C)	47	42.7
Hyperthermia (> 37.5 ^{o}C)	53	48.1
Hypoglycemia (< 45 mg %)	2	1.81
Shock (CRT >3sec)	17	15.4
Bleeding	24	21.8
Jaundice	18	16.3
Bulging Anterior Fontanelle	54	49.1

Interpretation: Most common clinical presentation in fungal septicemic neonates is feed refusal, apnoea, respiratory distress etc. Sign of meningeal involvement is bulging fontanelle.

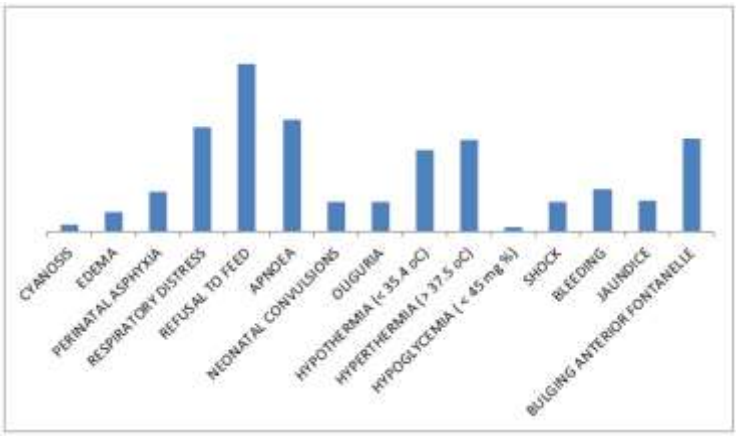

Fig-02: Clinical signs and symptoms observed in septicemic neonates.

DISCUSSION

Neonatal septicemia is considered the leading cause of infant mortality and morbidity. The frequency of infections in NICU varies from 6% to 25% in the United States and from 8% to 10% in Europe. There has been a wide variation in the growth positivity in India, as it is ranged from 16% to 54%. Early diagnosis and therapy are essential for the prevention of morbidity and mortality of neonatal sepsis in the neonatal intensive care unit. Presentation of sepsis varies depending on severity of the disease process and immune status of the neonate [6].

The common risk factors for fungal BSI include prematurity and very low birth weight (VLBW), central vascular catheterization, parenteral nutrition, use of broad spectrum antibiotics, H_2 blockers and corticosteroids, endotracheal intubation, and prolonged hospital stay. Neonatal fungal sepsis occurs in immunologically immature or very ill patients because of individual susceptibility and of health care related infection. An illustration from the National Nosocomial Infection Surveillance points out that the occurrence of these hospital acquired pathogens is greatest in extremely low birth weight infants (birth weight < 1000 g). The sources of candidiasis in NICU are often endogenous following colonization of babies with fungi. About 10% of these babies get colonized in the first week of life and up to 64 % babies get colonized by 4 weeks of hospital stay. Administration of contaminated intravenous solutions, notably the solution for total parental nutrition (especially the intra-lipid) may result in NICU outbreaks. Spread may also occur from patient to patient or through a colonized health care worker [3]. Broad-spectrum antibiotics (eg third generation cephalosporins) enhance fungal colonization by destroying competing bacterial flora. Similarly, mechanical ventilation is a likely risk factor for candidemia because the endotracheal tubes bypass normal mucociliary clearance, and the act of suctioning may promote bidirectional colonization of the respiratory and gastrointestinal tract. The presence and duration of central vascular catheter use is important in the development and management of neonatal candidiasis. Candida forms a thrombin sheath around the catheter to promote adhesion to the extracellular matrix. Other factors included exposure to third-generation cephalosporins, prematurity, lower birth weight, and delayed alimentation. Infants with birth weights < 750 g had a higher incidence of candidiasis than infants weighing 751 – 1000 g (11.4 % vs 3.4 %, respectively). Infants who received enteral feeding by day 3 of life developed candidiasis less frequently than those with delayed enteral feedings (3.4 % vs 8.7 %, respectively) [7].

Early signs of sepsis are non-specific and may present with episodes of fever, respiratory distress, diarrhea, low blood sugar level, decreased movements, decreased suckling, seizures, bradycardia, swollen belly area, vomiting, jaundice or rash. A heart rate above 160 can also be an indicator of sepsis, this tachycardia can present up to 24 hours before the onset of other signs.

The diagnosis can be made by complete workup including complete blood count with differential, blood culture, urinalysis, urine culture, and cerebrospinal fluid (CSF) studies and CSF culture. Culturing for microorganisms from a sample of CSF, blood or urine, is the gold standard test for definitive diagnosis of neonatal sepsis. Widespread infection despite negative culture is common [3]. It is often difficult to establish the diagnosis of fungal sepsis because there are no easy, reliable and rapid test that is why doctors have to attend to clinical signs and various laboratory findings. Although blood cultures have low sensitivity, they are still the "gold standard" to confirm the diagnosis of fungal sepsis. There are current investigations on non-culture diagnostic methods by polymerase chain reaction (PCR) test, but they are not fully standardized, nor have enough commercial assays yet [4].

In addition to fluid resuscitation and supportive care, Amphotericin B continues to be the mainstay of therapy for systemic fungal infections but its use is limited by the risks of nephrotoxicity and hypokalemia. Newer formulations of amphotericin B, namely the liposomal and the lipid complex forms, have recently become available and have been reported to have lesser toxicity. More recently Indian liposomal Amphotericin B derived from neutral lipids (L-Amp-LRC-1) has shown good response with less toxicity. Compared to other liposomal preparations, L-Amp-LRC-1 is effective at lower dose and is less expensive drug for the treatment of neonatal candidiasis.

SUMMARY AND CONCLUSION

Neonatal candidiasis is associated with significant morbidity and mortality. Blood culture, although not a sensitive test, remains the only reliable method for diagnosis. Although risk factors are known, the incidence of Candida varies greatly. This study indicated that the prevalence of neonatal sepsis was still high. Although, this study also tells that several factors like maternal age, multiple per vaginal examination, exclusive and immediate breastfeeding within an hour of delivery, put on Kangaroo mother care (KMC) within 1 hour, and age of the neonate are the factors affecting or predisposing neonates for sepsis. Mechanical ventilation > 5 days, central line >7 days, 20 % intra lipid infusion >7 days, use of > 2 broad spectrum antibiotics, prolonged hospital stay > 7 days and thrombocytopenia were the most common risk factor for fungal septicemia in our study. Based on this study we recommend strengthening of provision of health information on exclusive and immediate breastfeeding and KMC for mothers during postnatal and antenatal care services. Using Information Education Communication/ Behavior Change

Communication materials (posters, flip charts, wall paintings, manuals, brushers, and pamphlets) focused on breastfeeding and KMC to mobilize and sensitize the community. In addition, it should be recommended that the healthcare providers decrease multiple per digital vaginal examination as it is not indicated but better to be promoted. Prevention of risk factors in susceptible neonates with early removal of central line, timely fungal culture, Candida speciation and susceptibility testing are necessary for appropriate institution of treatment and better outcome. Frequent empirical use of fluconazole and amphotericin B may be avoided as it may lead to a shift in species distribution and higher antifungal resistance.

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