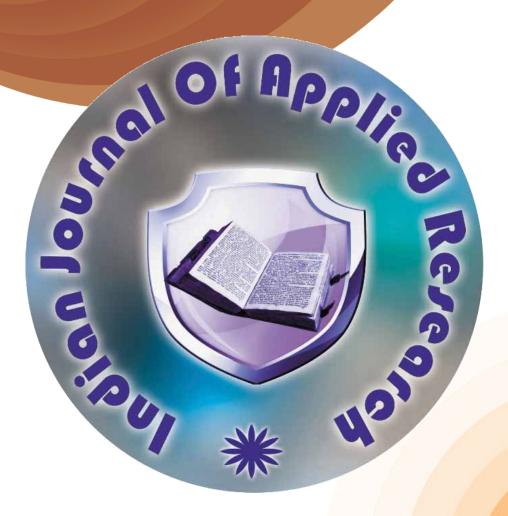
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Research Paper

Medical Science



A study of incidence and risk factors for neonatal systemic candidiasis

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ABSTRACT

Infection due to candida is the most common fungal infection in newborns whose defenses against infection may have been altered by diseases or therapy. Objective: To determine the incidence and to identify the risk factors associated with systemic invasive candida infection in NICU set up. Methods: This was prospective cohort study carried out at Neonatal Division, Department of Pediatrics, Sir Sayajirao General Hospital, Vadodara from December 2005 to October 2006. Results: Out of 579 admissions in intramural NICU, 63 (11% of NICU admissions) patients were included in the study. 7/63 (11.1%) patients (1.2% of total NICU admissions) had culture / smear positive for candida. 81% (51/63) were LBW. Approximately 85% (6/7) of patients who had evidence of candidal infection were LBW.

Leucopenia / neutropenia /abnormal I:T ratio, use of H2 blockers, parenteral nutrition and major gastro-intestinal surgery were most important risk factors for invasive candidal infection. Mortality amongst candida positive group was 6/7 (85.7%). Use of broad spectrum antibiotics, presence of DIC or thrombocytopenia were significant risk factors associated with invasive candidal infection among the extramural babies. Out of 6 patients studied from extramural NICU, 4 patients (66.7%) died. Conclusion: The incidence of candida infection was 11.1% (7/63). Leucopenia / neutropenia /abnormal I:T ratio, use of H2 blockers, use of parenteral nutrition, requirement of gastro-intestinal surgery, presence of NEC, use of broad spectrum antibiotics, presence of DIC / shock or thrombocytopenia were significant risk factors associated with invasive candida infection in this study. Keywords: neonatal systemic candidiasis, incidence, risk factors.

Keywords:

Neonatology has made significant advances in recent times and that has resulted in increased survival of very low birth weight (VLBW) and extremely low birth weight (ELBW) babies. Still infection remains the commonest cause of morbidity and mortality in newborns particularly in developing countries. Infection due to candida is the most common fungal infection in newborns whose defenses against infection may have been altered by diseases or therapy. Candida may cause severe and often fatal disseminated infection with involvement of almost all organs and systems of the body.

Candidal septicemia is very likely after the 3rd week of admission in VLBW babies who are mechanically ventilated or have undergone major abdominal surgery. Prematurity (gestational age <34 weeks), prolonged treatment with broad-spectrum antibacterials; particularly 3rd generation cephalosporins or carbapenems, use of H2-blockers has been implicated as factors predisposing to disseminated neonatal candidiasis. Prolonged endotracheal intubation, indwelling intravascular catheters or hyperalimentation fluids or other parenteral therapy may also contribute to infection with Candida. In addition, contaminated monitoring equipments and hands of NICU care givers may be a source of candida infection.

Objective: To determine the incidence and to identify the risk factors associated with systemic invasive candida infection in NICU set up.

Methods

A prospective cohort study was carried out at Neonatal Division, Department of Pediatrics, Sir Sayajirao General Hospital, Vadodara from December 2005 to October 2006. This is a tertiary care, 1100-bedded hospital, with average 400 deliveries conducted every month and average NICU admission rate of approximately 55/month.

Subjects

Inclusion Criteria-(1) Intramural (in-born) babies: All intramural babies fulfilling at least one of the following inclusion criteria were included in the study.

- Those who have received mechanical ventilation (IMV or CPAP mode) for duration of ≥ 24 hours.
- Clinical and/or serological evidence of sepsis after administration of broad-spectrum antibacterial drugs for ≥ 7 days.
- Any patient who had undergone major abdominal/thoracic surgery.
- Those having evidence of non-systemic fungal infection receiving broad-spectrum antibacterial drugs.

Inclusion Criteria- (2) Extramural (out-born) babies: During the study period, blood cultures were sent from extramural newborns with presence of risk factors and clinical suspicion of fungal sepsis and those who were found to be positive for candida were studied for risk factor analysis separately.

Data collection

Study included serial blood culture examinations and other supportive investigations.

- Sepsis screen: Sepsis screen was performed at the time of suspicion of sepsis (before administration of antibiotics) and was repeated at intervals according to the need.
- Total Leukocyte Count (TLC) and Differential Count (DC)
- Absolute Neutrophil Count (ANC) and Immature: Total neutrophil ratio (I:T)
- Serum- C- reactive protein(S-CRP) semi quantitative
- Platelet count
- CSF Examination was done in all cases of late onset sepsis and other symptomatic cases having lethargy, irritability, seizures, bulging fontanel or neck retraction.
- Collection of Blood Culture: As per NICU protocol, first blood culture was collected for culture and sensitivity in glucose broth in all the babies satisfying criteria for probable sepsis, before starting antibiotics. Subsequent blood cultures for Candida were collected from those babies fulfilling any of the inclusion criteria.

Culture for growth of fungi: On 3rd, 5th, 10th day, subcultures were done on sabouraud's dextrose agar (SDA) slants. The agar slants were incubated and were observed daily for growth. Typical creamy, smooth colonies with yeasty odor were produced as early as 24 hours and up to 3-4 days after inoculation when candida was present in the blood. If any of the 3 subcultures isolated the organisms, it was considered positive. Samples were declared negative if no growth observed on SDA slants within 7 days of last subculture.

Drug sensitivity testing could not be done due to limited facilities available at the Department of Microbiology at our hospital.

Other investigations

Chest roentgenogram was done in all cases of respiratory distress or requiring ventilatory care for other reasons. Ultrasound of Kidney and urinary system to evaluate for evidences of fungal infections. Urine Culture and sensitivity was done in suspected cases of urinary tract infection. In the event of death of study case, pathological autopsy was planned but could not be done in any case because of unavailability of parental consent.

Treatment plan

All the patients with positive sepsis screen were started with parenteral antibacterial drugs as per NICU protocol (Cefotaxime and Amikacin as 1st line during the study period) after collecting the blood culture. If the patient clinically worsened during the course of treatment with blood culture report awaited, change over to 2nd line antibacterial drugs (Piperacillin-Tazobactam) done empirically. In the event of availability of blood Culture and sensitivity report, change over of antibiotics was done according to sensitivity pattern.

Treatment was planned based on review of literature. Candida albicans infection was treated with Fluconazole and candida non-albicans infection was treated with Amphotericin B. Treatment was continued till at least one week after the last culture came negative.

Results

Out of 579 admissions in intramural NICU during the study period, 63 (11% of NICU admissions) patients were included in the study. 7/63 (11.1%) patients (1.2% of total NICU admissions) had culture / smear positive for candida. Three patients had blood culture positive for candida albicans, one had urine culture positive for candida albicans and three patients had only smear positive for candida albicans. These patients are referred as Candida Positive group and those who were negative (n=56) are referred to as Candida Negative group. Non albicans spp. was not isolated from any patient.

Among the study group, total 39 (62%) were male and 24 (38%) were female (Male: Female ratio of 1.62). 4/39 (10.3%)

of males and 3/24 (12.5%) of females were having invasive candida infection. There was no significant difference among either sex for predisposition to invasive candida infection. In our study more than half of the study population (32/63, 50.8%) was >37 weeks of gestational age. The rate of invasive candida infection was also closely correlated in this group, which was 75% (5/7).

81% (51/63) of those included in study (who fulfilled inclusion criteria) were LBW. Approximately 85% (6/7) of patients who had culture/ smear positive evidence of candidal infection were LBW. The major birth weight group involved with the invasive candidal infection was 2000-2499qms.

Table 1 shows that following risk factors had very strong association with development of invasive candida infection.

- 1. Leucopenia / Neutropenia / Abnormal I:T ratio
- 2. Use of parenteral nutrition
- 3. Requirement of gastro intestinal surgical procedure
- 4. Use of ranitidine (H2 Blockers)
- 5. Necrotizing enterocolitis (NEC)

Table: 1 RISK FACTOR ANALYSIS FOR INVASIVE CANDIDA INFECTION

Sr	Name of Risk factor	Fre- quency	P value (Fisher	Relative risk		Attribut- able risk %
No	140101	(N=7)	Exact Vaue)	Risk ratio	95% con- fidence interval	(Risk differ- ence)
1.	Gestational age < 35 wks	1	0.31	0.38	0.05-3.0	- 8
2.	Delay in BF/ MEF/Colostrum	6	0.6	1.4	0.18-10.6	3.4
3.	5 min APGAR <5	2	0.5	0.7	0.14-3.3	- 3.8
4.	Leucopenia / Neutropenia	3	0.007	8.7	2.65-28.5	53
5.	DIC / thrombocy- topenia / shock	6	0.42	2.04	0.26-15.7	6.5
6.	NEC	1	0.21	5.1	1.04-24.7	40
7.	Use of broad spectrum anti- biotics	6	0.19	3.45	0.4-2.7	11
8.	Use of ranitidine	6	0.03	7.0	0.9-55	18
9.	Requirement of mech. Ventila-tion	1	0.06	0.17	0.02-1.34	-15
10	Requirement of G.I. surgery	3	0.05	4.5	1.2-16.8	26
11	Use of parenter- al nutrition	2	0.01	12.2	5.2-28	92
12	Use of blood products	5	0.13	3.1	0.65-15	12

TABLE 2: OUTCOME ANALYSIS IN RELATION TO INVASIVE CANDIDA INFECTION:

OUTCOME					
Invasive candidal infection	LAMA	Dis- charged	Died	Total	
Candida positive group	1	0	6	7	
Candida negative group	2	26	28	56	
Total	3	26	34	63	

P value: 0.044

Table 2 shows that difference of outcome among two different groups, i.e. candida positive and candida negative is not by chance alone (P value 0.044). Mortality rate was 85.7% (6/7) among the patients showing evidence of invasive candidal infection, while it was 50% (28/56) among the other group and overall mortality rate of all study subjects was 54% (34/63).

This study also included the risk factors analysis for invasive candidal infection among extramural babies. During study period, total 6 newborns were detected to have culture/smear positive for candida. Out of these 6 cases, blood culture (BACTAC) was positive for candida albicans in two patients, blood

culture by routine method was positive for candida albicans in one patient for candida non-albicans in one patient. Urine culture was positive for candida albicans in two patients.

Drug sensitivity report was available in two cases (BACTAC), in both of those cases organism isolated was candida albicans and both were sensitive to amphotericin B and one of them showed resistance to fluconazole.

Out of 6 patients studied, 4 patients (66.7%) died. All the patients who died were having c-albicans isolated on blood culture.

Table 3: RISK FACTOR ANALYSIS FOR EXTRAMURAL BABIES

Name of risk factor	Frequency (n=6)	Percent- age	
Gestational age <35 weeks	1	16.6	
Delay in feeding	2	33.3	
5 minute APGAR < 5	1	16.6	
Leucopenia/ Neutropenia/ Abnor- mal I:T ratio	2	33.3	
DIC/Thrombocytopenia/ Shock	4	66.6	
Necrotizing Enterocolitis	2	33.3	
Broad spectrum antibacterials for > 7days	6	100	
Use of ranitidine	3	50	
Requirement of mechanical ventilation	2	33.3	
Major surgery required	2	33.3	
Use of parenteral nutrition	1	16.6	
Requirement of blood products	6	100	

As mentioned in Table 3, among the extramural babies, two risk factors; namely - use of broad spectrum antibiotics (especially 3rd generation cephalosporins & carbapenems) and use of blood products were consistently present in all cases. Apart from these two, presence of DIC, shock or thrombocytopenia was present in 66.7% of cases.

Discussion:

Most, but not all of our patients were LBW, this signifies the at risk nature of LBW babies in general with 85% of patients who had culture/ smear evidence of candida infection were LBW. Similar results of 73% rate of LBW among candida positive group was found in study by Malik GK et al from Lucknow.190% of patients from reference population were >37 weeks of gestational age and more than half of the study population was >37 weeks of gestational age. The rate of invasive candidal infection also closely correlated with both these groups, which was 75%. This finding is in contrast to the results of other studies which showed higher incidence among extreme preterms. 2,3,4

All the culture proven cases of candidemia were tested for differentiation of C. albicans from non-albicans. Non-albicans were not detected from any patient of intramural ICU. This is in contrast with the study done by Rani R.5 who had shown the changing trend of candidemia among neonates which was predominantly non-albicans infection. Poor association was found between gestational age less than or equal to 34 weeks and occurrence of invasive candidal infection in this study, though several other authors (Shetty SS et al2 and Saiman L et al6 from) found lower gestational age as significant risk factor.

During the study period, 25 neonates of gestational age <28 weeks were born but none of them could be included in the study because of very early mortality in that group. This can be explained by following confounding factors.

- a. High incidence of invasive candidal infection among the babies who required major gastrointestinal surgery (3/8), who were all of gestational age \geq 35 weeks.
- b. Because of affordability reasons, treatment options like surfactant administration, parenteral nutrition were used occasionally (Surfactant: 1 patient; Parenteral nutrition: 2 patients) and central venous catheter was not inserted in any patient. This may be the reason for decreased incidence of invasive candidal infection in preterms. Statistically significant association was found in our study with use of H2 blockers. This is considered as an important risk factor for development of invasive candidal infection in the literature7 and in prospective, multicentric study by Saiman L et al.6

Shetty SS et al. had got similar results as in our study and found abdominal surgery as a major risk factor for development of candidemia.2Significant association was found between use of parenteral nutrition and occurrence of invasive candidal infection.8

Prolonged use of 3rd generation cephalosporins is a well-known risk factor for candida.9 This was also seen in our study (babies from extramural NICU) where all patients had received broad spectrum antibiotics.

Conclusion:

In our study, the incidence of candida infection was 11.1% (7/63). Leucopenia / neutropenia /abnormal I:T ratio, use of H2 blockers, use of parenteral nutrition, requirement of gastro-intestinal surgery, presence of NEC, use of broad spectrum antibiotics, presence of DIC / shock or thrombocytopenia were significant risk factors associated with invasive candida infection in this study.

Recommendations:

Pediatricians should have clinical suspicion of candidiasis in view of high mortality rate. If patient receiving broad spectrum antibiotics does not show clinical / serological recovery, think about fungal infection. Suspect fungal sepsis, in patients who have undergone major G.I. surgery /NEC / or receiving TPN. Routine unnecessary use of H2 blockers should be avoided. Minimal enteral feeding should be started as early as possible. Infection prevention and control policy in NICU should be formulated / stepped up and periodically scrutinized to decrease fungal and resistant bacterial sepsis cases.

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