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Multidrug - Resistant Acinetobacter Species Infection among Neonates.

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ABSTRACT

Background: Multidrug resistant Acinetobacter infection has emerged as an important pathogen in neonatal sepsis in the recent years causing morbidity as well as mortality. **Methods:** Neonates admitted with sepsis in NICU from Jan 2014 to Dec.2014 were retrospectively analysed to find out the incidence, clinical features, antibiotic sensitivity pattern and the risk factors associated with mortality in culture positive Acinetobacter sepsis. **Results:** Incidence of neonatal sepsis was 11.3% (26/230).Neonatal sepsis caused by Acinetobacter spp was 5.65% (13/230). Pure growth of Acinetobacter was obtained in 13 and all of them were multidrug resistant. Resistance to Meropenem was 50%.Out of 13, six were early onset and seven were late onset sepsis. The major signs were poor perfusion (9/13), hypotension (9/13) and respiratory distress (13/13). Mortality due to Acinetobacter neonatal sepsis was 76.92% (10/13).The major risk factors associated with death in Acinetobacter sepsis were female sex, prematurity (<30 weeks) , birth weight less than 1500 gm and normal deliveries. **Conclusion:** Multidrug resistant Acinetobacter infection is fatal, particularly in premature and very low birth weight neonates.

Keywords: Acinetobacter sepsis, Mortality, Neonates.

INTRODUCTION

In India, according to the National Neonatal Perinatal Database (NNPD) 2000, the incidence of neonatal septicemia has been reported to be 24/1000 live births. Along with other organisms like Klebsiella spp., Staphylococcus aureus, E.coli, Pseudomonas spp. and Salmonella spp., Acinetobacter spp. are gaining importance as a potential pathogen in neonatal septicemia because of its frequent isolation, multidrug resistance and increased mortality.[1- 3]

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In general Acinetobacter is considered as an organism with low virulence but issues such as critical illness/ immunocompromised status, prematurity, low birth weight, endotracheal intubation, parenteral nutrition, intravascular catheterization and broad spectrum antibiotic therapy are known risk factors for Acinetobacter spp. Septicaemia.[4] The association between MDR Acinetobacter (MDRAB) and mortality is increasingly established in literature. [4,5,8-10,12,16] There is a dearth of literature identifying factors related to high mortality in neonates with Acinetobacter infection requiring high-level care. We therefore attempt to identify important risk factors associated with increased mortality in neonates with Acinetobacter sepsis.

MATERIALS AND METHODS

A retrospective analysis was performed over a period of one year (Jan 2014 TO Dec 2014) in a tertiary care hospital, after approval from the Institutional Ethics Committee. Inclusion criteria were neonatal sepsis cases with Acinetobacter species isolated from blood cultures. The case records of these neonates were analyzed retrospectively in a predesigned proforma by accessing the case papers from the medical record office (MRO) of the hospital. Various parameters like demography, mode of delivery, predominant signs and symptoms, risk factors, antibiotic sensitivity pattern, treatment and outcome were studied in them.

The present study included a total of 230 cases of suspected neonatal sepsis admitted to NICU. Blood samples of these neonates were collected with strict aseptic precautions and were processed by standard

bacteriological procedure for the isolation of causative organism.[9] We were unable to have complete subspecies data for Acinetobacter; therefore, we are reporting all Acinetobacter as the Acinetobacter spp. All culture positive neonatal sepsis cases were studied. Early onset sepsis was defined as sepsis within or at 72 hrs of birth and late onset sepsis as sepsis after 72hrs of birth. Multi-drug resistant Acinetobacter (MDR) was defined as resistant to more than three of the following seven drug classes: cephalosporins, carbapenems, ampicillin, fluoroquinolones, tetracyclines, chloromphenicols and aminoglycosides. "Pan-resistant Acinetobacter" was defined as resistant to all the above. Statistical analysis was done to study the association between various risk factors and Acinetobacter mortality.

RESULTS

Incidence of neonatal sepsis was 11.3% (26/230) and of Acinetobacter sepsis was 5.65% (13/230). Pure growth of *Acinetobacter* was obtained in all 13 neonates. Other 13 organisms isolated in the Non Acinetobacter group were Methicillin sensitive coagulase negative Staphylococi 5, Methicillin resistant coagulase negative Staphylococci 3,Enterococci 2,Methicillin sensitive Staphylococci, Pseudomonas, E.Coli, Klebsiella pneumoniae and Candida Albicans one each .

Table 1: Showing demographic features and clinical characteristics of Acinetobacter spp sepsis.

Variables		Number	%
Sex	Male	5	38.5
	Female	8	61.5
Birth weight	>1.5 kg	4	30.8
	<1.5 kg	9	69.2
Gestation	<30 weeks	9	69.2
	>30 weeks	4	30.8
Mode of delivery	Normal	8	61.5
	LSCS	5	38.5
Clinical and lab findings	Respiratory distress	13	100
	Poor perfusion	9	69.2
	Hypotension	9	69.2
	Feed intolerance	6	46.2
	Hypothermia	5	38.5
	Apnoea	2	15.4
	Convulsions	1	7.7
	Low platelets (<1 lac/mm^3)	7	53.8
Onset of sepsis	≤72 hours	6	46.2
	>72 hours	7	58.8
Duration between culture positivity and death	≤72 hours	8	80
	>72 hours	2	20
Length of hospital stay	≤ 7days	8	61.5
	> 7 days	5	53.8
Antibiotype	MDR	13	100
Outcome	Recovered	3	23.08
	Died	10	76.92

The major clinical signs were respiratory distress (13/13), poor perfusion (9/13), and hypotension (9/13).Mortality associated with Acinetobacter sepsis was 76.9 %(10/13). Duration between culture positivity and death was <3 days in 80% (8/10). All the Acinetobacter isolates were MDR .Pan resistance was found in 2 isolates.

Table 2: Prevalence of sepsis with respect to risk factors in cases with and without Acinetobacter.

Risk factor	groups	Total	Acinetobacter present		Acinetobacter absent	
			no.of cases	%	no.of cases	%
Sex	Male	11	5	45.5	6	54.5
	female	15	8	53.3	7	46.7
Birth weight	< 1.5kg	16	9	56.3	7	43.8
	>1.5kg	10	4	40.0	6	60.0
GA	<30 wk	14	9	64.3	5	35.7
	>30wk	12	4	33.3	8	66.7
Mode of delivery	Normal	21	9	42.9	12	57.1
	LSCS	5	4	80.0	1	20.0

Table 2 shows that prevalence of Acinetobacter cases is more than Non- acinetobacter cases in females, newborns with birth weight less than 1500gm and gestational age less than 30 weeks. As against this prevalence of Acinetobacter cases was less than Non Acinetobacter cases amongst males ,newborn with birth weight more than 1500 gm, gestational age more than 30 weeks and normal

delivery. However the difference was not statistically significant. Among LSCS cases, significantly more ($p<0.05$) cases of acinetobacter (80%) were observed as compared to non-acinetobacter cases (20%). Analysis of number of deaths in cases with Acinetobacter with respect to various risk factors is shown in **table3.**

Table 3: Distribution of death among cases with Acinetobacter with respect to risk factor.

Risk factor	groups	No. of cases	no of deaths	%	P value
Sex	male	5	2	40	0.043
	female	8	8	100	
Birth weight	≤ 1.5kg	9	8	88.9	0.043
	>1.5kg	4	2	50	
GA	≤30 wk	9	8	88.9	0.043
	>30wk	4	2	50	
Mode of delivery	Normal	9	8	88.9	0.043
	LSCS	4	2	50	

Table3 shows that Prevalence of deaths in cases with Acinetobacter sepsis was significantly more among females, birth weight ≤1500gm, gestational age ≤30weeks and normal deliveries as compared to males, birth weight more than 1500gm, gestational age more than 30 weeks and LSCS deliveries. Acinetobacter was isolated in 13 cases. Total 18 isolates were grown in different tissue samples; their distribution was as follows blood 11, cerebrospinal fluid 2, respiratory tract secretions3 and long line 2.

Table 4: shows resistance pattern to various antibiotics tested.

Antibiotic group	Antibiotics	Resistant(%)	Sensitive	Intermediate sensitivity
Penicillin	Ampicillin	18(100)	0	0
Aminoglycoside	Amikacin	17(94.44)	1	0
	Gentamycin	16(88.88)	2	0
Cephalosporins	Cefotaxime	17(94.44)	0	1
	Ceftriaxone	18(100)	0	0
	Cefipime	18(100)	0	0
Fluoroquinolones	Ofloxacin	16(88.88)	2	0
	Ciprofloxacin	17(94.44)	1	0
Carbapenem	Meropenem	9(50)	9	0
	Imipenem	11(61.11)	7	0
Sufamethaxazole trimethoprim		16(88.88)	0	2
Chloramphenicol		13(72.22)	4	1
Tetracycline		17(94.44)	1	0

High degree of resistance shown to various antibiotics used in our NICU was worrisome. Imipenem sensitivity was found more than Merpenem. The resistance found to Meropenem was 50%.see **Table 4**.

All the neonates were ventilated and had received empirical antibiotics in the NICU .The major antibiotic combinations given to the neonates were Ampicillin and Gentamycin in 38.5% cases (5/13) and Amikacin and Cefotaxime in 61.5 % cases (8/13).

Duration between culture positivity and death was <72hours in 8/13(61.5%) which indicates high virulence of the multi-drug resistant strain. Detailed analysis showed 7 patients received appropriate antibiotics for less than 48 hours before death (delay in giving appropriate antibiotics) and inappropriate use of antibiotics (use of antibiotic for which organism is not susceptible) in 4 cases of Acinetobacter sepsis.

DISCUSSION

In India, the incidence of Acinetobacter sepsis reported varies from 6.5% to 16.2%.[2, 3, 6-9] In the present study, the incidence was 5.65% which is lower than other reports from India.

Acinetobacter sepsis was found more in premature (76.9%) and very low birth weight babies (69.2%) which is similar to findings from other studies.[5,6,9,14] Preterm infants have a 3-10 fold higher incidence of infection than full term infants as they often require prolonged intravenous access, endotracheal intubation or other invasive procedures that provide a portal of entry for infection.[2, 4, 5, 9, 14]

Female sex was affected more commonly with ratio of 1.6:1 in our study which is similar to finding by Christo et al.[6] As against this, study from Mumbai shows more affection in male sex and term babies.[2]

Acinetobacter sepsis was found more in inborn babies born vaginally (69%) which is similar to other studies from India.[6-9] Acinetobacter is a known nosocomial pathogen and it is possible that newborns are being infected by hospital flora. Increasing rates of Acinetobacter infections may be due to lapses in infection- control practices. In these situations, "colonization pressure", which is a function of the proportion of patients already colonized or infected with Acinetobacter, can affect

the likelihood of cross-transmission between patients.[9, 16]

There was fairly even distribution between early onset and late onset sepsis in our study which is similar to findings from Kolkata study.[8] As against, most of the cases were early onset sepsis in studies from India and only one study from Turkey described late onset Acinetobacter sepsis.[1,2,14]

The symptoms seen in bacterial sepsis are irritability, lethargy, convulsions, reduced movements, fever, hypothermia, poor feeding etc. A characteristic finding in this study was respiratory distress, hypotension and poor perfusion [Table 1]. Similar observations were made in study from Karachi.[5] Respiratory distress, tachypnea, rib retractions were also reported in majority of the babies in studies from India.[2, 7, 9] and other parts of the world.[4,5,15] All the babies in our study had severe respiratory distress and were ventilated this observation is similar to study from Turkey were 20/21 babies were ventilated.[14]

In India, incidence of MDRAB range from 38% to 53.75%.[2, 8, 12] We found MDRAB is associated with increased mortality (76.9%) and morbidity (NICU stay >25 days) in babies that survived. These findings are similar to other studies from India and abroad. [2, 4, 5, 8, 10, 12-17] All the isolates in our study were MDRAB (100%).The details of the resistance are displayed in [Table 4]. Testing for colistin and Polymyxin B was not done.

A progressive decrease in effectiveness in third generation cephalosporins against Acinetobacter have been coupled with increased use of these antibiotics. Therefore cefotaxime and ceftazidime use should be discontinued where resistant strains for these antibiotics are being reported increasingly.[4, 12] Generally, imipenem is most active against A. baumanii. However, in a study by Cisneros and Rodriguez-Bano, imipenem susceptibility of A. baumanii isolates was 100% in 1991, which reduced to 50% in 2000.[17] Similar findings were observed in our study.Jaggi et al have described carbapenem resistance as high as 90% in their study from Harayana.[13] Therefore, we are left with only colistin / polymyxin B for the resistant cases.[3,5, 10, 13, 14] Unfortunately, testing for them was not available in our centre.Pan resistance was found in 2 isolates. Recent study from Karachi described Pan resistance (sensitive only to Colistin) in 71%.

In present study mortality was very high (76.9%). Female sex, prematurity ≤30 weeks, birth weight ≤1500gm and normal delivery were significant risk factors associated with increased mortality in our study($p<0.043$).These observations are similar to a study from Karachi which reported 47% mortality in their study.[5] Studies from India and other parts of the world have reported prematurity, low birth weight ,mechanical ventilation, presence of prolonged intravenous access(central or peripheral), infection with MDR within 7 days of admission, prior exposure to third generation cephalosporins and delay in starting appropriate antibiotics as significant risk factors associated with mortality.[2,4,5,7,10-12,15] In our study 69.2% of babies were preterm (≤30wk) with birth weight ≤1500gm, all had respiratory distress and were ventilated (100%), 53.84% acquired MDR Acinetobacter within 3 days after birth, there was prior use of cephalosporins in 61.5% cases, inappropriate use of antibiotics in 4 case and delay in 7cases. Study from Karachi described mortality due to neonatal Acinetobacter sepsis in 47% and 70% of them died within 4 days of acquiring infection.[5] In the present study 80%(8/10) newborns died within 3 days after positive culture.

Limitations of our study were that it was a single centre, short duration, retrospective study with limited number of cases. Sub analysis of Acinetobacter subspecies and testing sensitivity for colistin and polymyxin B was not done.

CONCLUSION

Multidrug-resistant Acinetobacter septicaemia may cause severe clinical disease in neonates that is associated with a high mortality. This study highlights the need for an effective infection control policy and rational antibiotic use in neonatal intensive care areas of each hospital in order to control neonatal sepsis due to Acinetobacter species. As MDR Acinetobacter strains are being increasingly isolated, antibiotics should be used judiciously, including the cephalosporins, fluoroquinolones and imipenem. Appropriate corrective measures should be taken at the earliest sign of MDR Acinetobacter infection in NICU to reduce the mortality associated with them.

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