Acinetobacter Sepsis Among Out-born Neonates Admitted to Neonatal Unit in Pediatric Emergency of a Tertiary Care Hospital in North India

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Abstract
Objectives To study the clinical profile, complications, antibiotic resistance pattern, treatment, and outcome of out-born neonates with Acinetobacter spp. sepsis admitted in Pediatric emergency of a tertiary care hospital in North India.

Methods In this subgroup analysis of a prospective study (conducted over 1 y, February 2018 through January 2019), neonates with Acinetobacter spp. sepsis were included. The data collection included demographic details, clinical features, pre-referral treatment, complications, antibiotic resistance pattern, treatment, and final outcome.

Results Acinetobacter spp. accounted for 10.6% (43/406) of all isolates and 22.7% (43/189) of Gram-negative isolates. The median (IQR) age at presentation was 1 (1–2) d, 2/3rd were male, and 46.5% were preterm. All were admitted in peripheral hospitals before referral to authors’ centre and all received intravenous antibiotics and fluids. The resistance to different antibiotics was: Ciprofloxacin 82%, cephalosporins 78–100%, amikacin 75%, piperacillin-tazobactum 62%, carbapenems 50–85%, chloramphenicol 83%, and tetracycline 50–60%. All isolates were sensitive to colistin. The survival rate was 37.2% (n = 16) and 62.8% (n = 27) had poor outcome [death and Left against medical advice (LAMA)]. Higher proportion of neonates with Acinetobacter sepsis had septic shock, multi-organ dysfunctional syndrome (MODS), and disseminated intravascular coagulation (DIC); and higher proportion required mechanical ventilation, vasoactive drugs, and had poor outcome compared to those with sepsis due to other organisms.

Conclusions Acinetobacter spp. accounts for high burden of sepsis among out-born neonates and is associated with alarmingly high resistance to cephalosporins, fluoroquinolones, aminoglycosides, piperacillin-tazobactum, tetracyclines, and carbapenems. Neonates with Acinetobacter spp. sepsis had higher rates of complications, requirement of mechanical ventilation and vasoactive drugs, and poor survival.

Keywords Out-born neonates · Antimicrobial resistance · Acinetobacter baumannii · MDR

Introduction

Neonatal sepsis is a clinical syndrome with systemic features of infection in first 28 d of life [1]. The incidence of neonatal sepsis in developing countries is higher than in developed ones. The incidence of culture positive neonatal sepsis in South Asia is 15.8 per 1000 live births, which is 2–4 times higher than in developed countries [1–4]. Sepsis is a leading cause of neonatal mortality accounting for 25–33% of neonatal deaths [1, 5–8] and culture positive neonatal sepsis has a mortality rate of 33–35% [1, 9]. The profile of pathogens causing neonatal sepsis in developing and developed countries is different. In developing countries, Gram-negative pathogens (>60%) are common isolates indicating horizontal transmission from environment or healthcare providers.
Whereas, group B Streptococci is predominant in developed countries [1].

Acinetobacter spp. is being recognized as a pathogen for neonatal sepsis leading to increased morbidity and mortality. Various studies demonstrated that Acinetobacter spp. accounts for 8–22% of blood culture positive neonatal sepsis [1, 10–20] and is among top 3 Gram-negative organisms causing neonatal sepsis along with Klebsiella spp., and Escherichia coli [1, 10, 17]. In the last decade, there is an increase in antimicrobial resistance (AMR) globally which can lead to increased morbidity, mortality, duration of hospital admission, and cost of treatment. Among Gram-negative organisms, 50–70% are now multi-drug resistant (MDR). Acinetobacter is often multi- or extensively-drug resistant. It has been demonstrated that, in India and South Asia, 78–91% of Acinetobacter spp. isolates were multi-drug resistant [1, 10, 17].

The data on profile of neonates with Acinetobacter sepsis and its antibiotic resistant pattern is limited from India. Therefore, this study was conducted to assess the clinical profile, risk factors, complications, antibiotic resistance pattern, treatment, and outcome of out-born neonates with Acinetobacter spp. sepsis admitted in Pediatric emergency of a tertiary level hospital in North India.

Material and Methods

This study was a subgroup analysis of a prospective study conducted in a newly established Neonatal Unit in Pediatric Emergency (NUPE) for out-born neonates in a tertiary care hospital in North India over 1 y (February 2018 through January 2019). Neonates (<28 d of postnatal age or <44 wk. of corrected gestational age, if born at <37 wk) with blood culture positive neonatal sepsis were enrolled. The study protocol of the prospective study was approved by Institute Ethics Committee and neonates were enrolled after written informed consent from parents or legal guardians. In this subgroup analysis, neonates with Acinetobacter spp. sepsis were enrolled.

NUPE is a 20 bedded area in Pediatric emergency with 8–12 admissions/day. The out-born neonates are referred from various hospitals in North Indian states and Union Territories (Chandigarh, Punjab, Haryana, Himachal Pradesh, Jammu and Kashmir, and Uttar Pradesh). The unit is staffed by 4–5 Junior Residents, 1–2 Senior Residents, 1–2 Consultants, and 4 Staff Nurses in each shift and has facilities for oxygen administration, continuous positive airway pressure (CPAP), mechanical ventilation, multipara monitors, infusion pumps, phototherapy units, double volume exchange transfusion, and retinopathy of prematurity (ROP) screening. The unit has services of Pediatric surgery, Pediatric cardiology, Cardiothoracic surgery, Radiodiagnosis, Ophthalmology, laboratory back-up, and blood bank. Once improved or stabilized, these neonates were either discharged or referred back to the referring unit or nearby special newborn care units (SNCUs).

Blood cultures were sent by the treating team whenever neonatal sepsis was suspected based on following clinical features: lethargy, apnea, seizures, poor feeding, temperature instability, tachypnea, retraction, tachycardia, hypotension, poor perfusion, maternal fever, prolonged rupture of the membranes for >24 h, foul-smelling or meconium-stained liquor, severe prematurity, or birth asphyxia necessitating active resuscitation [21]. The blood sample (1–2 ml) was obtained by using aseptic technique from peripheral vein into Pediatric BACTEC blood culture bottles which were immediately transported to the laboratory where they were incubated at 37 °C. Blood culture was performed using the BACTEC systems (Becton Dickinson, Maryland, USA). For any bottle which flagged positive, Gram staining was performed and subculture was done on appropriate media. Bottles were incubated in the system for 5 d and identification of organisms was done by Matrix assisted laser desorption ionization-time of flight [22].

Antimicrobial susceptibility of organisms was determined as per Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines by using Kirby-Bauer disc diffusion method [22]. The organisms were reported as susceptible/sensitive or resistant. In addition, the Gram-negative organisms were classified based on their resistance to various antibiotic classes: extended-spectrum cephalosporins (any two of cefazidime, ceftriaxone, or cefotaxime); aminoglycosides (any one of gentamicin or amikacin); fluoroquinolones (ciprofloxacin); piperacillin–tazobactam; carbapenems (imipenem or meropenem), and colistin [23].

The data was collected on pre-designed proforma regarding demographic details, perinatal risk factors for sepsis, place and mode of delivery, clinical features, and details of treatment at referring hospital (admission, intravenous fluids and antibiotics, oxygen support, and vasoactive drugs). The microbiological data included type of organisms (Gram-negative, Gram-positive, or yeast), individual organisms, and their resistant pattern. Based on time of onset, clinical course, and focus of infection the sepsis was classified into early- or late onset neonatal sepsis (EONS and LONS, respectively); and bacteremia, pneumonia, meningitis, urinary tract infection (UTI), or necrotizing enterocolitis (NEC). The treatment details (oxygen support, antibiotics, and vasoactive drugs), complications (pneumonia, thrombocytopenia, shock, acute kidney injury (AKI), meningitis, multiple organ dysfunction syndrome (MODS), healthcare associated infections (HCAIs), coagulopathy, disseminated intravascular coagulation (DIC), and NEC), final outcome [survival, death or left against medical advice (LAMA)], and duration of hospital stay were also recorded.

Blood culture positive neonatal sepsis was defined as isolation of a recognized pathogen from blood in neonates within 28 d of life suspected to have sepsis on the basis of clinical features or perinatal/maternal risk factors, along with
treatment involving appropriate antibiotics [10, 11]. EONS and LONS were defined as sepsis occurring within first 72 h of life and > 72 h of life, respectively [10, 17]. Shock was defined by the presence of impaired perfusion, requiring crystalloid bolus or support of vasoactive drugs [24]. AKI was defined as per KDIGO guidelines [25]. DIC was defined by the presence of thrombocytopenia (platelet count <150,000/ cumm) and coagulopathy [International normalized ratio (INR) >1.5 or activated partial thromboplastin time (aPTT) >35 s] [26]. MODS, NEC and HCAIs were defined as per standard guidelines [27–29].

The outcome of this study was to assess the clinico-microbiological profile of out-born neonates with *Acinetobacter spp.* sepsis and the resistant pattern of *Acinetobacter spp.*

Data entry and statistical analysis was performed using Microsoft Excel 2013 (Microsoft, Redmond, WA) and SPSS software version 21 (IBM Corp. 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Variables were described by descriptive statistics as percentages and median (IQR). Two groups were compared by Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. All tests were two-tailed and *p* value <0.05 was taken as significant.

### Results

Out of 406 neonates with blood culture positive sepsis, 189 (46.6%) grew Gram-negative organisms. Forty three neonates grew *Acinetobacter spp.* accounting for 10.6% of all isolates and 22.7% of Gram-negative isolates (Fig. 1). The age at presentation was 1 (1–2) d, 67.4% (n = 29) were males, birth weight was 2500 (1500–3000) g, and gestation was 37 (34–38) wk. Nearly half cases were preterm (46.5%, n = 20). Various antenatal risk factors for sepsis noted were leaking per vaginum, premature rupture of membranes, and meconium stained liquor (25.6%, n = 11 each) followed by maternal urinary tract infection (UTI) (16.3%, n = 7), and foul-smelling vaginal discharge (11.6%, n = 5). All were hospital born by normal vaginal delivery (58.1%, n = 25) or by Cesarean section (41.9%, n = 18). Most common clinical features noted were tachypnea (76.7%, n = 33), retraction (14%, n = 6), poor feeding and seizures (11.6%, n = 5 each) and lethargy, apnea, and temperature instability (9.3%, n = 4 each).

### Table 1

Baseline demographic, perinatal, and clinical variables

| Characteristics                          | Total cases (n = 43) |
|------------------------------------------|---------------------|
| Age at admission (days), median (IQR)    | 1 (1–2)             |
| Male, n (%)                              | 29 (67.4)           |
| Birth weight (grams), median (IQR)       | 2500 (1500–3000)    |
| Gestation (weeks), median (IQR)          | 37 (34–38)          |
| Preterm, n (%)                           | 20 (46.5)           |
| Low birth weight, n (%)                  | 19 (44.2)           |
| Antenatal risk factors for neonatal sepsis| 36 (69.8)           |
| Leaking per vaginum, n (%)               | 11 (25.6)           |
| Premature rupture of membranes, n (%)    | 11 (25.6)           |
| Meconium stained liquor, n (%)           | 11 (25.6)           |
| Maternal UTI, n (%)                      | 7 (16.3)            |
| Foul smelling discharge, n (%)           | 5 (11.6)            |
| Maternal antibiotics within 7 d of delivery, n (%) | 4 (9.3) |
| Maternal fever, n (%)                    | 3 (7)               |
| Chorioamnionitis, n (%)                  | 1 (2.3)             |
| Place of delivery                        |                     |
| Government hospital, n (%)               | 37 (86)             |
| Private hospital, n (%)                  | 6 (14)              |
| Mode of delivery                         |                     |
| Normal vaginal delivery, n (%)           | 25 (58.1)           |
| Cesarean section, n (%)                  | 18 (41.9)           |
| Neonatal resuscitation, n (%)            | 5 (11.6)            |
| Birth asphyxia, n (%)                    | 4 (9.3)             |
| Clinical feature                         |                     |
| Rapid breathing, n (%)                   | 33 (76.7)           |
| Retraction, n (%)                        | 6 (14)              |
| Poor feeding, n (%)                      | 5 (11.6)            |
| Seizures, n (%)                          | 5 (11.6)            |
| Lethargy, n (%)                          | 4 (9.3)             |
| Apnea, n (%)                             | 4 (9.3)             |
| Temperature instability, n (%)           | 4 (9.3)             |
| Poor perfusion, n (%)                    | 4 (9.3)             |

*UTI Urinary tract infection*
temperature instability, and poor perfusion (9.3%, \( n = 4 \) each) (Table 1).

Before referral to authors’ hospital, all neonates were admitted in local hospitals where they received intravenous fluids (97.7%), intravenous antibiotics (100%), mechanical ventilation (16.3%), and vasoactive drugs (11.6%) (Table 2).

The neonates with Acinetobacter spp. sepsis had EONS in 58.1% and LONS is 41.9% of cases. The A. baumannii accounted for 76.7% of isolates and A. junii for 23.3%. The resistant pattern of Acinetobacter spp. to different antibiotics is as: Ciprofloxacin 81.8%, cephalosporins 77.8–100%, cefoperazone+sulbactam 58.8%, amikacin 75%, piperillin-tazobactum 62.5%, carbapenems 50–84.6%, chloramphenicol 83.3%, and tetracyclines 50–60%. All the isolates tested were sensitive to colistin (Table 3 and Fig. 2).

The most common complications noted were shock (58.1%), thrombocytopenia (30.2%), MODS (20.9%), AKI (16.3%), pneumonia (14%), and meningitis (14%). In authors’ hospital, 11.62% (\( n = 5 \)) children received oxygen by nasal prongs, 16.3% (\( n = 7 \)) received CPAP, and 72.1% (\( n = 31 \)) underwent mechanical ventilation. All cases received intravenous antibiotics as shown in Table 4 and 58.1% (\( n = 25 \)) received vasoactive drugs. The survival rate was 37.2% (\( n = 16 \)) and 18.6% died and 44.2% went LAMA. The duration of hospital stay was 5 (2–9) d (Table 4).

Neonates with Acinetobacter spp. sepsis were younger; higher proportion had septic shock, MODS, and DIC; and higher proportion required mechanical ventilation, vasoactive drugs, and poor outcome (death and LAMA) compared with neonates with sepsis due to other organisms (other Gram-negative organisms, Gram-positive organisms and yeast, \( n = 363 \)) (Table 5).

### Discussion

The authors noted that Acinetobacter spp. accounted for 10.6% of all isolates and 22.7% of Gram-negative isolates causing sepsis among out-born neonates admitted to Pediatric emergency of a tertiary care hospital in North India. Acinetobacter spp. is an increasingly recognized pathogen causing neonatal sepsis and is responsible for high morbidity and mortality. Studies from India and South Asia demonstrated that Acinetobacter spp. accounts for 8–22% of blood culture positive neonatal sepsis and it is among top 3 Gram-negative organisms causing neonatal sepsis along with Klebsiella spp. and Escherichia coli [1, 10–20].

Along with the risk factors for neonatal sepsis (maternal fever, leaking per vaginum, premature rupture of membranes, gestation <37 wk, male sex, low birth weight, and need of artificial ventilation), out-born neonates, and prior hospitalization have been identified as strong risk factors for neonatal sepsis possibly due to inadequate infection control practices and irrational use of intravenous antibiotics at few or most of the places [4, 6, 8, 17]. Despite the fact that majority of neonates in the index study presented with EONS, the predominance of Gram-negative organisms as a cause of neonatal sepsis could be explained because all were out-born and were admitted in local hospitals where they received intravenous fluids, antibiotics, and mechanical ventilation. These factors favour acquisition of Gram-negative organisms.
horizontally from the healthcare environment or from healthcare providers as observed by other authors [1, 4, 10–12, 15].

The most worrisome data to share is the antibiotic resistant pattern of Acinetobacter spp. The resistance to commonly used antibiotics is alarmingly high (ciprofloxacin 81.8%, cephalosporins 77.8–100%, cefoperazone+subactam 58.8%, amikacin 75%, piperclillin-tazobactum 62.5%, carbapenems 50–84.6%, chloramphenicol 83.3%, and tetracyclines 50–60%). All the tested isolates were sensitive to colistin. Two recent studies with large sample size from North India demonstrated that the Gram-negative organisms showed high level of MDR [10, 17]. The resistance among Acinetobacter spp. to extended spectrum cephalosporins was in the range of 38–91.3%, carbapenems 78–93.3%, aminoglycosides 91.3%, and MDR 82–91.3%. The incidence of MDR strains was highest among A. baumannii (82–91.3%) followed by K. pneumonia 54–78%, E. coli 38–56.2%, and E. cloacae 50–65.2%. The prevalence of MDR among Acinetobacter spp. was noted to be higher among out-born neonates compared to in-born neonates (91% vs. 82%) [10, 17]. The rising AMR among common organisms causing neonatal sepsis (Gram-negative organisms, particularly Acinetobacter spp., Klebsiella spp., and E. coli) led to the resurgence in usage of colistin in the last decade and is going to pose a formidable threat in years to come [18–20].

The authors noted that the survival rate in neonates with Acinetobacter spp. sepsis was only 37.2% (n = 16) and rest 62.8% (n = 27) had poor outcome (death and LAMA). Also, neonates with Acinetobacter spp. sepsis were younger, had higher rate of complications (septic shock, MODS, and DIC); and higher proportion required mechanical ventilation, vasoactive drugs, and had worse outcome (death and LAMA) when compared to sepsis caused by other organisms (Table 5). The mortality due to neonatal sepsis could be as high as 25–35% and it rises to 23–50% in those with culture-proven sepsis [1, 10, 16, 17]. It has been demonstrated that case fatality rate in neonates with Acinetobacter spp. sepsis is as high as 38–59% [10, 17], similar to the poor outcome in the index study.
The strengths of this study include prospective nature of data collection over 1 year period from a newly established unit for out-born neonates from North India. Since most of the neonates were out-born and referred from different healthcare facilities, the results of this study can apply to a large population of neonates from all the healthcare facilities in surrounding states. The authors recorded the clinical details, microbiological data, and clinical outcome. The results are significant addition to literature from India. The limitations of the study include single centre study, small sample size, and no long-term follow-up. There was lack of information about other markers of sepsis (total leucocyte count, total neutrophil count, immature to mature neutrophil ratio, C-reactive protein, procalcitonin, cytokines etc) [30].

### Conclusions

*Acinetobacter* spp. accounts for high burden of sepsis among out-born neonates admitted to Pediatric emergency. Resistance to fluoroquinolones, cephalosporins, aminoglycosides, carbapenems, chloramphenicol, and tetracyclines is alarmingly high. All isolates were sensitive to colistin. Neonates with *Acinetobacter* spp. sepsis were younger, had more complications, higher requirement of mechanical ventilation and vasoactive drugs, and had poor survival.

### Authors’ Contributions

SM: Data collection, statistical analysis, initial draft of manuscript; SKA: Conceptualized the study, literature review, critically reviewed and finalized the manuscript; RS: Statistical analysis, and review of manuscript; VS: Conceptualized the study and provided inputs for data collection; VSM and VG: Microbiological investigations. SKA will act as guarantor for this paper.

### Compliance with Ethical Standards

**Conflict of Interest** None.

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**Table 5** Outcome in neonates with *Acinetobacter* sepsis when compared to sepsis caused by other organisms (other Gram -ve, Gram +ve and yeast, n = 363)

| Variables                          | *Acinetobacter* (n = 43) | Others organisms (n = 363) | p value |
|-----------------------------------|--------------------------|---------------------------|---------|
| Age at admission (days), median (IQR) | 1 (1–2)                 | 2 (1–3)                   | 0.02    |
| Male, n (%)                       | 29 (67.4)                | 231 (63.6)                | 0.83    |
| Birth weight (grams), median (IQR) | 2500 (1500–3000)        | 2200 (1600–3100)          | 0.62    |
| Gestation (weeks), median (IQR)   | 37 (34–38)               | 37 (33–38)                | 0.94    |
| Preterm, n (%)                    | 20 (46.5)                | 162 (44.6)                | 0.56    |
| Admission in peripheral hospital, n (%) | 43 (100)            | 348 (95.9)                | 0.39    |
| IV fluids, n (%)                  | 42 (97.7)                | 305 (84)                  | 0.42    |
| Antibiotic, n (%)                 | 43 (100)                | 347 (95.6)                | 0.23    |
| Mechanical ventilation, n (%)     | 7 (16.3)                 | 40 (11)                   | 0.44    |
| Vasoactive drugs, n (%)           | 5 (11.6)                 | 65 (17.9)                 | 0.31    |
| Shock, n (%)                      | 25 (58.1)                | 131 (36.1)                | 0.01    |
| Thrombocytopenia, n (%)           | 13 (30.2)                | 159 (43.8)                | 0.08    |
| MODS, n (%)                       | 9 (20.9)                 | 34 (9.4)                  | 0.02    |
| AKI, n (%)                        | 7 (16.3)                 | 45 (12.4)                 | 0.56    |
| DIC, n (%)                        | 5 (11.6)                 | 14 (3.8)                  | 0.02    |
| HCAI, n (%)                       | 4 (9.3)                  | 31 (8.5)                  | 0.34    |
| NEC, n (%)                        | 2 (4.7)                  | 15 (4.1)                  | 0.87    |
| Required mechanical ventilation, n (%) | 31 (72.1)           | 139 (38.3)                | 0.000   |
| Required vasoactive drugs, n (%)  | 25 (58.1)                | 121 (33.3)                | 0.002   |
| Poor outcome (Death and LAMA), n (%) | 27 (62.8)            | 134 (36.9)                | 0.002   |
| Duration of hospital stay, days median (IQR) | 5 (2–9)                | 6 (3–8)                   | 0.50    |

**AKI** Acute kidney injury; **DIC** Disseminated intravascular coagulation; **HCAI** Healthcare associated infections; **IQR** Interquartile range; **LAMA** Left against medical advice; **MODS** Multi-organ dysfunction syndrome; **NEC** Necrotizing enterocolitis

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