

# Disseminated Staphylococcal Disease in Neonates Admitted to Pediatric Emergency of a Developing Economy: Clinicomicrobiological Profile, Management, and Outcome

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## ABSTRACT

**Aim:** To report clinical and microbiological profile, complications, management, and short-term outcome of neonates with disseminated staphylococcal disease.

**Materials and methods:** This retrospective study was conducted in pediatric emergency of a tertiary-care teaching hospital in North India involving 26 outborn neonates admitted with diagnosis of disseminated staphylococcal disease over 1-year period (January–December 2018).

**Results:** Majority of the neonates presented between day 7 and day 28 of life with mean duration of illness of 6.6 (2.4) days. The risk factor for disseminated staphylococcal disease was noted in 38.5% ( $n = 10$ ) cases (intramuscular injection, venous cannula, nonpenetrative trauma, and umbilical line). Skin and subcutaneous tissue abscesses were the commonest localization (88.5%) followed by pneumonia (30.8%), meningitis (26.9%), septic arthritis (19.2%), and osteomyelitis (11.5%). *Staphylococcus aureus* was isolated in 53.8% cases, and methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 71.4% of isolates. Common complications were acute kidney injury, respiratory failure, and shock (in 26.9% each) and venous thrombosis and septic ileus (in 7.7% each). The duration of appropriate antibiotics was 16.5 (6.4) days. Incision and drainage of abscesses was done in 53.8% cases, 19.2% underwent arthrotomy, 27% needed vasoactive drugs, and 19% received invasive mechanical ventilation. The duration of hospital stay was 17.7 (8.7) days, and mortality was 15.4% ( $n = 4$ ).

**Conclusion:** Disseminated staphylococcal disease is common in neonates. The skin and soft tissue focus with hematological spread to distant organs lead to fulminant disseminated disease. High index of suspicion, early diagnosis, prompt appropriate antibiotics, and early surgical debridement are integral part of management. The MRSA contributes to significant burden.

**Keywords:** Abscesses, Methicillin-resistant *Staphylococcus aureus*, Neonates, *Staphylococcus aureus*.

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## INTRODUCTION

*Staphylococcus aureus* is a well-known pathogen causing a wide spectrum of infections in children and adults in tropics and subtropics, ranging from minor skin infections to fatal systemic and disseminated disease.<sup>1</sup> The varied presentation of staphylococcal infection and disseminated staphylococcal disease in pediatric population has been highlighted in several studies.<sup>2–6</sup> The management of disseminated staphylococcal disease consist of prompt diagnosis, timely and appropriate antibiotics, prompt surgical drainage of collections, cardiorespiratory monitoring, and supportive care.<sup>5,6</sup> The reported mortality in children with staphylococcal bacteremia ranges from 1.4% to 30–35%.<sup>1,2,7</sup> A decade ago, experience about the clinical and microbial profile, critical care needs, management, and outcome of children admitted to pediatric intensive care unit with diagnosis of disseminated staphylococcal disease from our center was published.<sup>5,6</sup>

Neonates are predisposed to staphylococcal infection, and risk factors include prematurity, low birth weight, prolonged hospitalization, and presence of invasive devices.<sup>8</sup> However, data about disseminated staphylococcal diseases in neonates are scanty. Therefore, we conducted this retrospective study over a period of 1 year to review the demographic, clinical, and microbial features; management issues; and short-term outcome of neonates with disseminated staphylococcal disease.

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## MATERIALS AND METHODS

This retrospective study was conducted in neonatal unit for outborn neonates in pediatric emergency [neonatal unit in pediatric emergency (NUPE)] of a tertiary-care teaching hospital in North India over a period of 12 months (January–December 2018). Outborn neonates (<28 days of postnatal age or <44 weeks corrected gestational age if born at <37 weeks) who were admitted in pediatric emergency during study period with diagnosis of disseminated staphylococcal disease were enrolled.

Admission files were retrieved from medical record department, and data were recorded on a predesigned study pro forma. The data regarding demographic variables such as age, sex, gestation, birth weight, mode of delivery, and perinatal details were recorded. Details regarding current illness including presenting complaints, duration of illness, treatment details in referring hospital, and risk factors for disease were recorded. Disease localization, laboratory parameters, microbiological details, complications related to disease, treatment details (antibiotics, surgical interventions, vasoactive drugs, and mechanical ventilation), duration of hospital stay, and final outcome (survived or death) were also noted.

Disseminated staphylococcal disease was defined as pyogenic infection of two anatomically noncontiguous organs and/or culture of *Staphylococcus aureus* or demonstration of clustered gram-positive cocci from at least one normally sterile body fluid.<sup>5,6</sup> Acute kidney injury (AKI) was defined as per KDIGO guidelines.<sup>9</sup> Septic shock was defined by the presence of impaired perfusion requiring crystalloid bolus or inotropic support.<sup>10</sup> Disseminated intravascular coagulation was defined by the presence of thrombocytopenia and coagulopathy (INR > 1.5 or aPTT > 35 seconds).<sup>11</sup> Anemia was defined as hemoglobin <11 g/dL, leukocytosis as total leukocytic count >15,000/cumm, and thrombocytopenia as platelet count <150,000/cumm.<sup>12</sup>

NUPE has 20 beds with 8 to 12 admissions per day. The unit caters to outborn neonates who were referred to us from various hospitals in and around Chandigarh. At any time, there are 40 to 50 outborn neonates admitted in the unit (2–3 neonates on a single cot). In each shift, there are four to five junior residents, one to three senior residents, one to two consultants, and three staff nurses managing the unit. There are facilities for oxygen and CPAP administration, monitoring by pulse oximetry, infusion pumps, phototherapy, orogastric feeding, double volume exchange transfusion, and ROP screening. Recently, the unit is equipped with eight ventilators (for noninvasive and invasive ventilation). The unit has radiodiagnosis, pediatric surgery, pediatric cardiology, cardiothoracic surgery, ophthalmology, laboratory back-up, and blood bank services. Neonates are being referred from government and private hospitals in Chandigarh, Punjab, Haryana, Himachal Pradesh, Jammu and Kashmir, and Uttar Pradesh. Once stabilized, these neonates are either discharged or back referred to the referring unit or nearby sick newborn care units. After discharge, neonates are followed in pediatric outpatient department in our center.

### Statistical Analysis

Data entry and statistical analysis was performed on Microsoft Excel 2010 (Microsoft, Redmond, WA) and SPSS software version 20 (SPSS, Inc, Chicago, IL). Descriptive statistics [mean, standard deviation (SD), median, range, and percentages] was used for baseline variables.

## RESULTS

### Patient Characteristics and Clinical Features

During the study period, 26 neonates with disseminated staphylococcal disease were enrolled. Majority of the cases were males and were born at term gestation (70% each). The birth weight was 2,673 g, almost all were delivered vaginally, and 15.4% ( $n = 4$ ) had birth asphyxia (Table 1).

The mean age was 25 (10.9) days, and the majority presented between day 7 and 28 of life. The duration of current illness was 6.6 (2.4) days, and most common symptoms were pustules or abscesses, fever, irritability, rapid breathing, and diarrhea. The risk factor for disseminated staphylococcal disease was noted in the

**Table 1:** Clinical characteristics and localization of infection in neonates with disseminated staphylococcal disease

Characteristics	Total cases, $n = 26$
Age at presentation (in days), mean (SD)	25.1 (10.9)
<7 days, $n$ (%)	1 (3.8)
7–14 days, $n$ (%)	4 (15.4)
14–21 days, $n$ (%)	5 (19.2)
21–28 days, $n$ (%)	14 (53.8)
>28 days, $n$ (%)	2 (23.1)
Male, $n$ (%)	18 (69.3)
Term gestation, $n$ (%)	18 (69.3)
Mode of delivery	
Vaginal delivery, $n$ (%)	25 (96.2)
LSCS, $n$ (%)	1 (3.8)
Birth weight (in g), mean (SD)	2,673 (772)
Duration of illness (in days) mean (SD)	6.6 (2.4)
Symptoms	
Pustules, abscesses, $n$ (%)	23 (88.5)
Fever, $n$ (%)	16 (61.5)
Irritability, $n$ (%)	12 (46.1)
Rapid breathing	5 (19.2)
Diarrhea, $n$ (%)	2 (7.6)
Risk factors	
Intramuscular injection, $n$ (%)	4 (15.4)
Presence of cannula, $n$ (%)	4 (15.4)
Trauma, $n$ (%)	2 (7.6)
Presence of umbilical line, $n$ (%)	2 (7.6)
Prior hospitalization, $n$ (%)	22 (84.6)
Duration of stay (in days), mean (SD)	9.9 (3.8)
Prior antibiotic use, $n$ (%)	20 (76.9)
Duration of antibiotics, mean (SD)	8.5 (2.9)
Localization of infection	
Abscesses, $n$ (%)	23 (88.5)
Lower limb, $n$ (%)	11 (47.8)
Head and neck, $n$ (%)	8 (34.8)
Upper limb, $n$ (%)	7 (30.4)
Liver, $n$ (%)	3 (13.1)
Pneumonia, $n$ (%)	8 (30.8)
Meningitis, $n$ (%)	7 (26.9)
Septic arthritis, $n$ (%)	5 (19.2)
Osteomyelitis, $n$ (%)	3 (11.5)

form of intramuscular injection at the site where abscess developed later on (15.4%,  $n = 4$ ), presence of cannula at the site (15.4%,  $n = 4$ ), nonpenetrative trauma at local site, and presence of umbilical line in two each (7.6%) (Table 1).

Twenty-two (84.6%) neonates were admitted in the hospital before being referred to us for preexisting or current illness for a duration of 9.9 (3.8) days, and 76.9% ( $n = 20$ ) received antibiotics for 8.5 (2.9) days (Table 1).

### Localization of Infection

The commonest type of infection was skin and subcutaneous tissue abscesses and deep abscesses (88.5%,  $n = 23$ ). The common site of involvement was lower limbs (47.8%), followed by head and neck region (34.8%), upper limbs (30.4%), and liver (13.1%). Other noncontiguous organs involved were in form of pneumonia (30.8%), meningitis (26.9%), septic arthritis (19.2%), and osteomyelitis (11.5%).

### Laboratory Investigations and Microbiological Profile (Table 2)

Results of routine investigations are shown in Table 2. Anemia was noted in 73.1% ( $n = 19$ ) cases with mean hemoglobin 10.6 g/dL, leukocytosis in 89%, and thrombocytopenia in 42% cases. Half of the cases had hyponatremia (with mean sodium of  $134.9 \pm 5.8$  mEq/L) and 42.3% ( $n = 11$ ) had hypoalbuminemia (mean albumin  $3.3 \pm 0.6$  g/dL). The *Staphylococcus aureus* was isolated in 53.8% cases and methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 71.4% and methicillin-sensitive *Staphylococcus aureus* (MSSA) for 28.6% of isolates.

**Table 2:** Laboratory investigations and microbiological profile

Laboratory investigations	Total patients ( $n = 26$ )
Hemoglobin (g/dL), mean (SD)	10.6 (3.3)
Anemia (Hb <11 g/dL), $n$ (%)	19 (73.1)
Total leukocytic count (per cumm), mean (SD)	22,049 (8,024)
Leukocytosis (TLC >15,000/cumm), $n$ (%)	23 (88.5)
Absolute neutrophil count (per cumm), mean (SD)	15,873 (5,139)
Absolute lymphocyte count (per cumm), mean (SD)	7,140 (3,270)
Platelet count (per cumm), mean (SD)	3,54,500 (1,16,998)
Thrombocytopenia (platelet count <1.5 lac/mm <sup>3</sup> , $n$ (%)	11 (42.3)
Hyponatremia (serum sodium <135 mEq/L), $n$ (%)	13 (50)
Hypoalbuminemia (serum albumin <3.5 g/dL), $n$ (%)	11 (42.3)
CRP (mg/L), mean (SD)	85.9 (43.1)
Microbiological profile	
Staphylococcus isolated, $n$ (%)	14 (53.8)
MRSA, $n$ (%)	10 (71.4)
MSSA, $n$ (%)	4 (28.6)
Pus Gram stain positive for <i>staphylococcus</i> , $n$ (%)	7 (26.9)
Pus culture positive for <i>staphylococcus</i> , $n$ (%)	12 (46.2)
Blood culture positive for <i>staphylococcus</i> , $n$ (%)	6 (23.1)

Pus Grams stain showed gram-positive cocci in clusters in 26.9% ( $n = 7$ ) cases; and pus and blood culture grew *Staphylococcus aureus* in 46.2% ( $n = 12$ ) and 23.1% ( $n = 6$ ) cases, respectively. Three cases had pus Gram stain, pus culture, and blood culture positive; four had only pus Gram stain and pus culture positive; four had only pus culture positive; two had only blood culture positive; and one had both pus and blood culture positive. About 64% isolates were resistance to ciprofloxacin and 57% resistant to clindamycin. All isolates were sensitive to vancomycin, teicoplanin and linezolid.

HIV serology, immunoglobulin profile, dihydrorhodamine assay, and lymphocyte subset failed to show any abnormality in these cases. Echocardiography was done in all cases, and there was no evidence of infective endocarditis or pericardial effusion.

### Complications (Table 3)

Acute kidney injury, respiratory failure, and shock was noted in 26.9% ( $n = 7$ ) cases each; venous thrombosis and septic ileus in 7.7% ( $n = 2$ ) cases each; and only one case had DIC (Table 3).

### Course in Hospital and Outcome (Table 4)

The antibiotics received were combination of cefotaxime or ciprofloxacin and amikacin in 65.4% ( $n = 17$ ) of cases, vancomycin in 69.2% ( $n = 18$ ), cloxacillin in 53.8% ( $n = 14$ ), and meropenem in 38.5% ( $n = 10$ ) cases for a duration of 16.5 [6.4] days. Initial antibiotics were changed in 58% of cases based on culture sensitivity reports. Surgical interventions needed in form of incision and drainage of skin and subcutaneous abscesses in 53.8% and arthrotomy in 19.2% ( $n = 5$ ). Three cases had subcentemetric liver abscesses that were not amenable to any surgical intervention. Infusion of vasoactive drugs were needed in 26.9% ( $n = 7$ ) cases for a mean duration of 56.3 hours, and 19.2% ( $n = 5$ ) required invasive ventilation for a mean duration of 45.8 hours. The duration of hospital stay was 17.7 (8.7) days. The mortality rate was 15.4% ( $n = 4$ ) (Table 4).

Respiratory failure and shock (seen in 27% of cases) were independently associated with increased mortality ( $p$  value = 0.002 for both). Invasive ventilation was required about one-fifth of cases and associated with increased mortality ( $p$  value = 0.0003). Isolation of MRSA was not associated with higher mortality ( $p$  value = 0.79) (Table 4).

## DISCUSSION

We reported 26 neonates with disseminated staphylococcal disease. Skin and subcutaneous abscesses were the commonest localization of infection followed by pneumonia, meningitis, osteomyelitis, and septic arthritis. Predisposing conditions were seen in less than half of cases. *Staphylococcus* was isolated in 53.8% cases and MRSA accounting for 71.4% of isolates. Respiratory

**Table 3:** Various complications noted in neonates with disseminated staphylococcal disease

Complications	Total patients ( $n = 26$ )
Hypoalbuminemia (serum albumin <3.5 g/dL), $n$ (%)	11 (42.3)
Acute kidney injury, $n$ (%)	7 (26.9)
Respiratory failure, $n$ (%)	7 (26.9)
Shock, $n$ (%)	7 (26.9)
Venous thrombosis, $n$ (%)	2 (7.7)
Septic ileus, $n$ (%)	2 (7.7)
DIC, $n$ (%)	1 (3.8)

**Table 4:** Treatment details and outcome of neonates with disseminated staphylococcal disease

Treatment	Total patients (n = 26)
<b>Antibiotics</b>	
Cefotaxime + amikacin, n (%)	12 (46.2)
Ciprofloxacin + amikacin, n (%)	5 (19.2)
Cloxacillin, n (%)	14 (53.8)
Vancomycin, n (%)	18 (69.2)
Meropenem, n (%)	10 (38.5)
Duration of antibiotics (in days), mean (SD)	16.5 (6.4)
<b>Discharged on oral antibiotics</b>	
Linezolid	5 (19.2)
Cloxacillin	4 (15.4)
Cefpodoxime	3 (11.5)
<b>Surgical intervention</b>	
Incision and drainage, n (%)	14 (53.8)
On day of hospital stay, mean (SD)	3 (2.4)
Arthrotomy, n (%)	5 (19.2)
On day of hospital stay, mean (SD)	3.4 (3.8)
<b>Vasoactive drugs, n (%)</b>	
Duration (in hours), mean (SD)	56.3 (17.6)
<b>Ventilation, n (%)</b>	
Duration (in hours), mean (SD)	45.8 (14.7)
<b>Duration of hospital stay (in days), mean (SD)</b>	
17.7 (8.7)	
<b>Outcome</b>	
Recovered, n (%)	22 (84.6)
Death, n (%)	4 (15.4)

failure, shock, and AKI were noted in one-third of cases. The duration of intravenous antibiotics was around 2 weeks, half of the cases needed incision and drainage, one-fourth needed vasoactive drugs, and one-fifth needed mechanical ventilation. The duration of hospital stay was 21/2 weeks, and mortality was 15%. This is first study involving neonates with disseminated staphylococcal disease.

*Staphylococcus aureus* is a well-known pathogen in pediatric as well as neonatal population to cause skin and subcutaneous abscesses, blood stream infections, and other deep-seated abscesses. Disseminated staphylococcal disease is reported in children associated with high mortality and morbidity. In the preantibiotic era, it was as high as 80%, which has decreased to about 20%.<sup>13,14</sup> The literature on neonatal disseminated staphylococcal disease is scarce. Risk factors for staphylococcal disease include trauma, immunocompromised status, presence on invasive devices, and chronic medical illness.<sup>15</sup>

Other interesting findings of this study are as follows: most of the cases were term born and presented after first week of life with >50% in fourth week of life. Since our hospital is a tertiary-care teaching institute, over 80% of cases had prior hospital stay and similar number received parenteral antibiotics prior to referral. Anemia was also quite prevalent, affecting nearly three-fourth of cases and could be due to nutritional cause, sampling losses, or as a part of illness. Thrombocytopenia was seen in 40% of cases. Half of the cases had hyponatremia, probably secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). AKI was seen in 27% cases and was nonoliguric and none required renal

replacement therapy. All these complications became passive at time of discharge.

Drug resistance is a major problem with *Staphylococcus aureus*.<sup>16</sup> Prevalence of MRSA is highly variable from 17 to 56%, while that of VRSA is <14%.<sup>17-19</sup> We noted a high prevalence of MRSA (71.4%) probably due to the fact that majority of cases were referred to us from different hospitals and had majority had received antibiotics for more than a week. These isolates could be hospital acquired. We were not able to isolate organism in about half of the cases probably due to the fact that majority of the cases had received parenteral antibiotics prior to referral. The recent reports of rising MRSA in community is worrisome issue.<sup>20</sup>

The treatment of disseminated staphylococcal disease include early initiation of appropriate antibiotics per local sensitivity pattern after collection of appropriate samples for culture, removal of foci of infection, and aggressive source control.<sup>5,6</sup> Predictors of morbidity and mortality include positive blood cultures persisting for >48 hours, persistent fever, implanted device, skin lesions, immunosuppression, and multiorgan involvement.<sup>20</sup> In index study, appropriate antibiotics were used for about 2 weeks, half required incision and drainage of abscesses, and 20% needed arthrotomy. The overall outcome was good, with 85% survival rate. We did not note any pleural or pericardial suppurative complications. In contrast, Baranwal et al.<sup>5,6</sup> noted that in children with disseminated staphylococcal disease (n = 53), the pleuropulmonary disease was there in 89% and pericardial effusion in 40%.

Hieber et al.<sup>2</sup> reported 15 children with disseminated staphylococcal disease and 13 had cutaneous manifestations. Authors noted that an absolute neutrophil count >10,000/cumm and band forms >500/cu mm were predictors of disseminated disease and the mortality was 27%. Kabra et al.<sup>3</sup> reported 10 children with disseminated staphylococcal disease. The involved organs include skin and respiratory system in 80%, liver in 70%, and pericardial effusion in 50%. MSSA was the commonest isolate (80%). The average duration of hospital stay was 32 days and mortality 20%. There were no identifiable predisposing factors and no predictors of mortality were identified. Half of the cases had history of minor trauma. Common systems involved were musculoskeletal system followed by respiratory system. Organism could be isolated in 78%, and of them 12% were MRSA. Median hospital stay was 15 days, and mortality rate was 8.6%. Mandal et al.<sup>21</sup> noted that in 36 children with disseminated staphylococcal disease, blunt trauma was the commonest precipitating factor, all isolates were MRSA, and 89% demonstrated vancomycin resistance. From our institute, Baranwal et al.<sup>5,6</sup> reported 53 children with disseminated staphylococcal disease. Fever and respiratory distress were the commonest presentation. Pleuropulmonary and pericardial involvement was much higher (89% and 40%, respectively), whereas we did not notice any pleural or pericardial involvement. MSSA accounted for 91% of isolates (40 of 44 isolates), whereas we noticed increased prevalence of MRSA (70%). Complications were much more prevalent in their cohort when compared to index study (shock 90% vs 27%, need for invasive ventilation 32% vs 19%). The mortality is 13.2% (10/53) as in our study (15%, 4/26). Presence of both septic shock and need for mechanical ventilation were associated with high mortality (RR, 20.5; p < 0.001), similar to index study.

The strengths of this study are that this is the first study to document clinicomicrobiological profile, complications, management, and outcome of neonates with disseminated

staphylococcal disease. The limitations include retrospective nature of the study. The data on long-term follow-up of these cases is not available. The information whether the organisms were community acquired or hospital acquired is not available. We assumed that majority were hospital acquired, as majority of the cases came to us from other hospitals.

## CONCLUSION

Disseminated staphylococcal disease is an underreported disease in neonates. When compared to the pediatric population, complication rates were less, but mortality seems to be similar. MRSA is the predominantly isolated pathogen. High index of suspicion, early diagnosis, prompt appropriate antibiotics, and early surgical debridement are integral part of management.

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