The predictors of outcome and progression of pediatric sepsis and septic shock: A prospective observational study from western India

Shah S, Deshmukh CT, Tullu MS

ABSTRACT
Introduction: There is a paucity of studies on the progression and outcome of Systemic Inflammatory Response Syndrome (SIRS) with its determinants. Aims and Objectives: To determine the predictors of the outcome and progression of pediatric sepsis and septic shock. Materials and Methods: Prospective observational study of children fulfilling criteria of SIRS and their progression to sepsis, severe sepsis, and septic shock (clinically and biochemically) was conducted at a tertiary care center. Results: Totally, 200 children were recruited over a period of 21 months (from February 2016 to October 2017). Most cases (80, 40%) were infants. Of the total, 188 (94%) cases were of an infective etiology (mostly respiratory system). Temperature and heart rate were the two commonest SIRS parameters which were deranged. Blood cultures were positive in only 25 (12.5%) cases. Out of the total 200 children, 108 progressed to sepsis, of which 26 progressed to severe sepsis, of which 22 progressed to septic shock. Abnormal leukocyte count, culture positivity and severe acute malnutrition were significantly associated with progression of SIRS patients to septic shock ($P = 0.001$, 0.00001 and 0.002, respectively). Factors associated with mortality were positive blood culture, multiorgan dysfunction, late hospital admissions, severe acute malnutrition, and requirement of supportive care ($P$ values $<0.0001$, $<0.0001$, 0.03, $<0.0001$ and $<0.0001$, respectively). Conclusions: SIRS can progress to septic shock if not identified early. The predictors of mortality were positive blood cultures, multiorgan dysfunction, late hospital admissions, severe acute malnutrition, and requirement of supportive care. The predictors of progression to septic shock were abnormal leukocyte count, culture positivity, and severe acute malnutrition.

KEY WORDS: Blood culture, intensive care unit, malnutrition, mortality, multiple organ dysfunction

Introduction

Pediatric sepsis remains as a major cause of mortality and morbidity worldwide. It includes a clinical spectrum of severity - Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis, septic shock and multi-organ failure. It is important to identify the determinants that predict the progression and mortality in SIRS, so as to deal with such patients in a timely manner. There are very few Indian studies conducted on such determinants.[1] The earlier studies from India and abroad have given a few determinants of outcome/mortality.[2-4] There was a need to comprehensively study these and other determinants from the Indian population. Hence, we decided to conduct the present study. Our aims and objectives were to study the determinants [age, sex, number of SIRS parameters met, specific SIRS parameters met, system involved at primary diagnosis, blood culture positivity, use of supportive care (including mechanical ventilation, blood transfusion, antibiotics, and others)] with outcome and progression of pediatric sepsis and septic shock.
and inotropic support), anemia, clinical rickets, severe acute malnutrition and multiorgan dysfunction of outcome and progression (to sepsis, severe sepsis or septic shock) in SIRS patients admitted in our department.

### Materials and Methods

The study was conducted over a period of 21 months (from February 2016 to October 2017) in the Department of Pediatrics of a tertiary care hospital affiliated to a medical college from a metropolitan city of Western India. The study protocol was approved by the Institutional Ethics Committee and patients were enrolled in the study after written informed consent from the parent/guardian. Assent was obtained from children aged 7–12 years. Our department has an approximate of 4200 admissions annually with about 550 admissions to Pediatric intensive care unit (PICU). All children (1 month to 12 years) admitted on the days selected for the study were screened for SIRS. Table 1 gives the definitions for various terms as given by International Pediatric Sepsis Consensus Conference by Goldstein et al.\(^6\) which were used in the present study. The participants for the study were recruited on 3 days of the week (Monday, Wednesday, and Friday) and only when the student investigator was available (on call). “Late hospital admissions” were those patients who presented after 14 days of the onset of the illness. All the required parameters were recorded in a predesigned patient case record form. Patient’s clinical notes and investigations were assessed on a day to day basis till the patient was discharged or until death. The various determinants studied to predict the outcome and progression of SIRS were age, sex, number of SIRS parameters met, specific SIRS parameters met, system involved at primary diagnosis, blood culture positivity, use of supportive care (mechanical ventilation, blood transfusion, and inotropic support), anemia, clinical rickets, severe acute malnutrition, and multiorgan dysfunction. The outcome measures studied were duration of hospital stay, survival, and mortality. Taking into consideration, the previous year’s admissions meeting the criteria of SIRS, previous studies conducted\(^6\)–\(^8\) and the formula given below, the sample size for this study was calculated. Formula used - \(n = \frac{Z^2 \times p(1-p)}{e^2}\), where \(n = \) sample size, \(p = \) prevalence of the disease, \(d = \) precision of 5%, \(z = z\)-value at 5% significance and \(e = \) range of confidence.

### Table 1: Definitions for various terms used in the present study\(^5\)

| Terminology used                      | Definition                                                                                       |
|---------------------------------------|-------------------------------------------------------------------------------------------------|
| **A. Systemic inflammatory response syndrome (SIRS)** | 2 out of following 4 criteria to be met, 1 of which must be abnormal temperature or abnormal leukocyte count:  
1. Core temperature >38.5°C or <36°C (rectal, bladder, oral or central catheter),  
2. Tachycardia: Mean heart rate > 2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli; OR; Unexplained persistent elevation of heart rate over 0.5-4 hour; OR In children < 1 year old, persistent bradycardia over 0.5 hour (mean heart rate < 10th percentile for age in absence of vagal stimuli, beta-blockers or congenital heart disease),  
3. Respiratory rate > 2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia, and  
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils. |
| **B. Sepsis**                         | SIRS plus a proven or suspected infection.                                                      |
| **C. Severe sepsis**                  | Sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic).  
1. Cardiovascular organ dysfunction defined as:  
Despite >40 ml/kg of isotonic intravenous fluid in 1 hour - Hypotension ≤ 5th percentile for age or systolic blood pressure <2 SD below normal for age; OR Need for vasoactive drug to maintain blood pressure; OR  
2 of the following 5:  
- Unexplained metabolic acidosis: Base deficit >5 meq/L  
- Increased arterial lactate: > 2 times upper limit of normal  
- Oliguria: Urine output <0.5 ml/kg/hour  
- Prolonged capillary refill: >5 sec  
- Core to peripheral room temperature gap >3°C.  
2. Acute respiratory distress syndrome (ARDS) was defined by - the presence of a PaO2/FiO2 ratio ≤300 OR PaCO2 >65 torr or 20 mm Hg over baseline PaCO2 OR Need for non-elective invasive or noninvasive mechanical ventilation  
3. Organ dysfunctions (neurological, renal, hepatic or hematologic) was defined as -  
(i) Neurological: GCS score of <or=11 or acute change in mental status with Glasgow Coma Score (GCS) of > or =3 points from abnormal baseline.  
(ii) Renal: Serum creatinine of >2 times upper limit of normal for age or 2 fold increase in baseline creatinine.  
(iii) Hepatic: Total bilirubin >or=4 mg/dl or alanine transaminase level twice the upper limit of normal for age.  
(iv) Hematological: Platelet count of less than 80,000 or a 50% decline in the platelet count from the highest value recorded over the last 3 days or INR >2. |
| **D. Septic shock**                   | Sepsis plus cardiovascular organ dysfunction (as defined above).                                |
interval. Hence, the estimated sample size was 200. Association between qualitative variables was assessed by Chi-Square test and Fisher’s Exact test. Comparison of quantitative data by outcome among the cases (death and discharge) was done using Mann-Whitney Test and comparison by degree of sepsis was done by Kruskal-Wallis one-way analysis of variance on ranks. Regression analysis was used to determine the predictors of outcome.

**Results**

During the study period, 200 patients fulfilled the inclusion criteria and were enrolled [Figure 1]. Of the total, 113 (56.5%) were males and 87 (43.5%) females with a male to female ratio of 1.3:1. Most were infants (<1 year; 80 cases-40%) followed by the age group of 2 to ≤4 years (36 cases-18%) while 26 cases (13%) belonged to 4 to ≤6 years age group. From the remaining cases, 21 (10.5%) cases were between 1 to ≤2 years and 37 (18.5%) belonged to the school age group (6–12 years). Of the total, 181 cases were discharged while 19 cases expired. Mortality was 9.5%. While 188 (94%) of patients had an infective etiology, only 12 (6%) had a non-infective etiology. The non-infective group mainly involved hyper reactive airway disease (5 cases), pancreatitis (2 cases), Kawasaki disease (2 cases), and poisonings (3 cases). All patients of non-infective etiology were discharged. Most cases had primary diagnosis belonging to the respiratory system (100 cases; 50%), followed by central nervous system (35 cases; 17.5%) and cardiovascular system (22 cases; 11%). Other primary diagnosis belonged to the genitourinary system (15 cases; 7.5%), gastrointestinal system (5 cases; 2.5%), and dengue (13 cases, 6.5%). Other cases (10 cases; 5%) included poisonings, cellulitis, and inborn error of metabolism.

For cases to fit the criteria of SIRS, minimum of 2 criteria were to be met with one criteria being abnormal temperature or abnormal leukocyte count. In our study, 85 (42.5%) patients fulfilled 3 criteria, 72 (36%) patients fulfilled 4 criteria, and 43 (21.5%) patients met 2 criteria. Most common parameters met were abnormal temperature (180 cases; 90%) and abnormal heart rate (165 cases; 82.5%). Of the total, 92 cases (46%) remained in SIRS; remaining 108 patients progressed to sepsis; of these 26 progressed to severe sepsis; of which 22 progressed to septic shock shown in the flowchart [Figure 2]. Severe acute malnutrition was seen in 60 (30%) of the 200 cases. Co-morbidities like anemia and clinical rickets were noted in 126 (63%) and 50 (25%) of cases respectively. Only 25 out of 200 cases (12.5%) had positive blood cultures. The patient characteristics are depicted in Table 2. The most common organisms isolated included gram negative bacilli (pseudomonas) followed by gram positive organisms (staphylococcus aureus). Out of the total 20 urine cultures sent, 7 were positive (3 Candida glabrata, 2 Klebsiella pneumoniae and 2 E. coli). Out of 10 CSF (cerebrospinal fluid) cultures sent, one was positive for Klebsiella pneumoniae. Of the total, 93% cases were administered antibiotics (89.5% within the first hour of admission). Multi organ dysfunction (>2 organ dysfunction) was seen in 20 (10%) cases. Inotropes were required in 27 (13.5%) patients, fluid boluses were given to 44 (22%) patients, mechanical ventilation was required in 26 (13%) patients and blood transfusion was required in 83 (41.5%) patients.

Various patient parameters were correlated with the outcome. On univariate analysis, positive blood cultures ($P = 0.000000027$), presence of severe acute malnutrition ($P = 0.0000988$), multiorgan dysfunction ($P = 0.0000000000257$), progression

**Table 2: Characteristics (clinical and laboratory) of study group**

| Characteristics (Clinical and Laboratory) | Present n (%) | Absent n (%) |
|-------------------------------------------|---------------|--------------|
| Abnormal temperature                      | 180 (90)      | 20 (10)      |
| Abnormal heart rate                       | 165 (82.5)    | 35 (17.5)    |
| Abnormal respiratory rate                 | 138 (69)      | 62 (31)      |
| Abnormal leukocyte count                  | 150 (75)      | 50 (25)      |
| Anemia                                    | 126 (63)      | 74 (37)      |
| Clinical rickets                          | 50 (25)       | 150 (75)     |
| Severe acute malnutrition (SAM)           | 60 (30)       | 140 (70)     |
| Positive blood cultures                   | 25 (12.5)     | 175 (87.5)   |

Figures in parenthesis indicate percentage.

![Figure 1: Enrollment details for study population](image1.png)

![Figure 2: Progression of SIRS](image2.png)
to septic shock ($P = 0.0046$) and presence of an underlying congenital heart disease ($P = 0.0000003$) were found to be significantly associated with a poor outcome. Those cases needing mechanical ventilation ($P < 0.0001$) and inotropic support ($P < 0.0001$) were also associated with a poor outcome [Table 3]. Other factors like age, gender, number of SIRS parameter met, anemia, and clinical rickets did not affect the outcome significantly. Further, on subjecting the parameters to binominal regression analysis, severe acute malnutrition, multiorgan dysfunction, and delayed presentation to the hospital were found to be significantly associated with a poor outcome.

Similarly, various patient factors were correlated with progression of SIRS to septic shock. Among these, abnormal leukocyte count, positive blood cultures, and presence of severe acute malnutrition were found to be statistically significant [Table 4]. Other factors like age, gender, number of SIRS parameter met, anemia and clinical rickets did not affect the progression significantly. Also, other SIRS parameters like abnormal temperature, heart rate, and respiratory rate were not found to be significantly associated with the progression.

**Discussion**

Sepsis is an important cause of morbidity and mortality in children. Hence, it is important to identify sepsis in the early stages to prevent its progress. In our study, the predictors of mortality included positive blood cultures, multiorgan dysfunction, late hospital admissions, severe acute malnutrition and requirement of supportive care. The predictors of progression to septic shock were abnormal leukocyte count, culture positivity, and severe acute malnutrition.

The incidence of SIRS was higher in infants followed by children in the age group 2–4 years. This can be explained by the fact that infants have a weaker immune system and poor response to any antigen. This is also the age group more prone to respiratory infections. This finding is similar to the study by Watson RS et al [7] and Khan M.R. et al. [11]. However, in the study by Pavare J et al. [9] the maximum SIRS incidence was in the age group 2–5 years. In our study, 188 cases of SIRS were having infection as a cause (94%), whereas only 12 cases (6%) had a non-infective etiology. Similar pattern of infective and non-infective cases were seen in other studies [like Ganjoo S, et al. [6] -79% (n = 159) patients with infection associated SIRS and 21% (42 cases) with non-infective SIRS; and Carvalho PRA et al. [8] - 64% (n = 194) cases due to infectious etiology and 36% (n = 110) were non-infectious]. In our study, primary diagnosis of most cases of infective and non-infective SIRS belonged to the respiratory system (n = 100; 50%). These findings were similar to the studies by Kurade A, et al. [1] Weiss SL, et al. [11] and Watson RS et al. [7].

**Table 3: Correlation of risk factors (at admission) with outcome (univariate analysis)**

| Parameters                              | Death (n = 19) | Discharged (n = 181) | Chi square Value | $P$  |
|-----------------------------------------|---------------|---------------------|------------------|------|
| Abnormal temperature at the time of admission | 16 (84.2%)    | 164 (90.6%)         | 0.782            | 0.377|
| Abnormal heart rate at the time of admission | 16 (84.2%)    | 149 (82.3%)         | 0.043            | 0.837|
| Abnormal respiratory rate at the time of admission | 15 (78.9%)    | 123 (67.9%)         | 0.971            | 0.324|
| Abnormal leukocyte count                | 15 (78.9%)    | 135 (74.6%)         | 0.174            | 0.676|
| Anemia                                  | 14 (73.7%)    | 112 (61.9%)         | 1.028            | 0.311|
| Rickets                                 | 05 (26.3%)    | 45 (24.9%)          | 0.019            | 0.889|
| Severe acute malnutrition               | 15 (78.9%)    | 45 (24.9%)          | 23.952           | 0.0000988*|
| Positive blood cultures                 | 10 (52.6%)    | 15 (8.3%)           | 30.91            | 0.00000027*|
| Underlying congenital cardiac illness    | 10 (52.6%)    | 12 (6.6%)           | 37.167           | 0.0000003*|
| Presence of septic shock                | 16 (84.2%)    | 06 (3.3%)           | 12.27            | 0.00046*|
| Need for mechanical ventilation         | 16 (84.2%)    | 10 (5.5%)           | 94.131           | 2.95E-22*|
| Need for inotropic support              | 16 (84.2%)    | 11 (6.1%)           | 89.89            | <0.0001*|
| Multiorgan dysfunction                  | 11 (57.9%)    | 9 (4.9%)            | 53.51            | 0.0000000000257*|

* $P$ significant (<0.05) by Chi square test (univariate analysis); Figures in parenthesis indicate percentage

**Table 4: Correlation of various parameters with progression to septic shock (univariate analysis)**

| Parameters                              | Progressed to septic shock (n = 22) | Did not progress (n = 178) | $P$  |
|-----------------------------------------|-------------------------------------|---------------------------|------|
| Abnormal temperature                    | 18 (82%)                            | 162 (91%)                 | 0.277|
| Abnormal heart rate                     | 21 (95.5%)                          | 144 (80.9%)               | 0.391|
| Abnormal respiratory rate               | 18 (81.8%)                          | 128 (71.9%)               | 0.360|
| Abnormal leukocyte count                | 17 (77.3%)                          | 133 (74.7%)               | 0.001*|
| Positive blood cultures                 | 12 (54.5%)                          | 13 (7.3%)                 | 0.00001*|
| Anemia                                  | 16 (72.7%)                          | 110 (61.8%)               | 0.134|
| Severe acute malnutrition               | 17 (77.3%)                          | 43 (24.2%)                | 0.002*|
| Clinical rickets                        | 05 (22.7%)                          | 45 (25.3%)                | 0.508|

* $P$ significant (<0.05) by Chi square test (univariate analysis); Figures in parenthesis indicate percentage
Two of the four criteria (abnormal temperature or abnormal leukocyte count mandatory) need to be fulfilled in order to label a case to have SIRS. In our study, out of the 200 cases, 85 (42.5%) patients fulfilled 3 criteria, 72 (36%) fulfilled 4 criteria and 43 (21.5%) patients met 2 criteria. Of all the criteria, most presented with fever (180 cases; 90%) followed by tachycardia (165 cases; 82.5%). In the study by Ganjoo S, et al. diagnosis of SIRS was mostly based on abnormal temperature with increased respiratory rate. Abnormal total leukocyte count and tachypnea were the most commonly observed parameters by Kurade A, et al. and fever with abnormal temperature were most commonly noted by Pavare J, et al.

Out of 200 patients with SIRS in our study, severe acute malnutrition (SAM) was seen in 60 (30%) of the cases. In the study by Kaur et al. weight for age less than 80% was not found to be significantly associated with a poor outcome. Chisti et al. noted a much higher case fatality among under-five SAM children with pneumonia and severe sepsis who required fluid resuscitation in addition to standard antibiotic and other supportive therapy compared to those without severe sepsis.

Positive blood cultures were seen in 12.5%, urine cultures in 3.5% and CSF cultures in 0.5% of the cases. Culture positivity rates have varied across different studies. Khan et al. had a slightly higher culture positivity (blood cultures- 27 cases, 20.3%; urine cultures- 2 cases, 1.5%; and CSF cultures- 1 case, 0.8%) compared to our study. Ramya A, et al. had a culture positivity of 4.4% (coagulase negative staphylocoeci and klebsiella pneumoniae) whereas Kurade A, et al. had a culture positive rate of 18.6% (staphylococcus most common). Our lower positive cultures may be due to the receipt of antimicrobials prior to arrival to our hospital and use of non-Bactec techniques.

The mortality in our study was 9.5% (19 cases). A study conducted in Pakistan by Khan et al. had a mortality of 24% in sepsis patients. Since our study included patients from the stage of SIRS, mortality is slightly lesser. Similar to our study, other studies also correlated various parameters with the outcome of patients. Kur et al. observed that multiorgan dysfunction and need for inotropic agents were found to be associated with a poor outcome (similar to our study) whereas it was anemia and leucopenia in the study by Kurade et al. Organ dysfunction (>2 organs), PRISM III score >10 and need of >2 inotropes were predictors of mortality in a study conducted by Khan et al. The comparison of various predictors of outcome as seen in our study with those seen in other studies is depicted in Table 5.

There are not many studies on factors assessing progression of SIRS to septic shock. In our study, abnormal leukocyte count, positive blood cultures, and presence of severe acute malnutrition were significantly associated with the progression. Patients with the above should be monitored and treated promptly to prevent the progression. The strengths of our study included prospective enrollment, adequate sample and meticulous follow-up for determining predictors for progression as well as the outcome. The limitations of our study included our inability to correlate the clinical findings with investigations (like C-reactive protein, procalcitonin and lactate levels). Also, serological tests for viral/fungal infections were not always possible due to non-availability of these tests in our hospital and financial constraints. The number of positive blood cultures were lesser when compared to the number of cases of suspected sepsis.

In everyday clinical practice, one of the major challenges is to recognize sepsis when it starts. In its early stages, sepsis is often mistaken for a milder infection or a condition resulting from some other therapeutic or surgical cause. Being the most vulnerable part of the population, Pediatric patients require special attention as sepsis is one of the common causes of death. Worldwide escalation of the awareness of sepsis is the key point to early detection and timely antibacterial treatment, which leads to better survival with both good early and late-term outcomes.

As SIRS criteria lack specificity, new Sepsis 3 guidelines have been introduced in adults in 2016. This defines sepsis as a dysregulated host response manifested as an organ dysfunction. The qSOFA (quick Sequential Organ Failure Assessment) score has been used in adults to predict sepsis. This included 3 parameters: altered sensorium, systolic blood pressure and respiratory rate. This has not yet been commonly used in the pediatric population. A retrospective study conducted by van Nassau et al. in Netherlands showed that the score showed moderate prognosis in determining the PICU transfer and mortality of children admitted with suspected bacterial infection. Since these “Sepsis 3” guidelines were not yet laid for the pediatric population at the time of enrollment of patients in our study, we used the definitions laid by International Pediatric Sepsis Consensus Conference. The newer avenues for future research may include use of the qSOFA (prospectively) in the pediatric population, as well as studies on other laboratory determinants of progression and outcome including like procalcitonin and other biomarkers.

To conclude, most patients remained in SIRS in our study. Most cases had an infective etiology with respiratory system most commonly involved. The factors associated with a poor outcome were—positive blood cultures, multiorgan dysfunction, late hospital admissions, severe acute malnutrition, and requirement of supportive care. Factors found to be significantly associated with progression of SIRS were abnormal leukocyte count, culture positivity, and severe acute malnutrition.

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Conflicts of interest
There are no conflicts of interest.

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Table 5: Comparison of predictors of mortality with various studies

| Details of the study | Factors found to be significantly affecting the mortality | Parameters not found to be significantly affecting mortality |
|----------------------|----------------------------------------------------------|----------------------------------------------------------|
| Present study (2017); Mumbai, India; 200 cases; Prospective study. | Univariate analysis- (i) Positive blood cultures (ii) Severe acute malnutrition (iii) Multiorgan dysfunction (iv) Presence of underlying congenital heart disease (v) Septic shock (vi) Use of mechanical ventilation and inotropic support. Multivariate analysis- (i) Severe acute malnutrition (ii) Multiorgan dysfunction (iii) Delayed presentation to the hospital. | (i) Age and Sex (ii) Number of SIRS parameters met on admission (iii) Anemia (iv) Rickets (v) Specific SIRS parameter met. |
| Kaur G, et al. (2017); Haryana, India; 50 cases; Prospective study. | Univariate analysis- (i) Multiorgan dysfunction (ii) Septic shock (iii) Mean PRISM III score (iv) Duration of mechanical ventilation (v) Anemia (vi) Inotropic support. | (i) Positive blood cultures (ii) Age and Sex (iii) Urban residence (iv) Weight for age <80% (v) Duration of ward stay prior to PICU transfer (vi) ≥1 fluid bolus prior to PICU transfer. |
| Kurade et al. (2016); Sangli, India; 94 cases; Prospective study. | Univariate analysis- (i) Anemia (ii) Leucopenia (iii) Need for mechanical ventilation (iv) Decompensated shock. | (i) Age and Sex (ii) Thrombocytopenia (iii) Coagulopathy (iv) Multiorgan dysfunction (v) Inotrope required. |
| Khan MR, et al. (2007-2008); Karachi, Pakistan; 133 cases; Retrospective study. | Univariate analysis- (i) PRISM III score >10 (ii) Organ dysfunction (>2 organs) (iii) >1 inotrope used. | (i) Age (ii) Sex (iii) Culture proven infection (iv) Length of stay >2 days (v) Presence of septic shock. |

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