Comparison of sepsis definitions in a resource poor environment

Subhashchandra R. Daga^{a,*}, Hilary Klonin^b, Minoti D. Ayarekar^a, Santosh K. Joshi^a and Sanjay B. Janwale^a

^a*Department of Pediatrics, B.J. Medical College and Sassoon General Hospital, Pune, India*

^b*Pediatric Intensive Care Services, Hull Royal Infirmary, Hull, UK*

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Abstract. Sepsis is an important cause of childhood death in developing countries. The International Pediatric Sepsis Consensus Conference (IPSCC) guidelines for definition has five categories and requires complex information, which may be difficult to access in resource poor settings, possibly leading to under-diagnosis and problems with triage, referral and documentation for public health assessments. We aimed to provide a workable system for grading sepsis categories, assess this against the IPSCC definition and use this information to guide further adaptations. We conducted a prospective observational study of consecutive admissions to a pediatric intensive care unit of a public hospital between August and September 2006. We recorded history and demographic, clinical, investigative, treatment and outcome details. We compared the performance of the IPSCC scoring system to the modified system. We studied one hundred consecutive admissions and collected data for the modified format. The distribution of sepsis cases and (deaths) was as follows: systemic inflammatory response syndrome 26 (2), sepsis 30 (5), severe sepsis/septic shock 15 (11), organ dysfunction 2 (2) and no sepsis 27 (3). Overall mortality was 23%. Despite its simplicity, the modified system corresponded well to the IPSCC system except for the systemic inflammatory response syndrome category. We suggest adaptations to improve agreement with IPSCC whilst maintaining ease of use. It is possible to simplify the IPSCC score to provide information in a resource poor setting but only further studies will be able to assess robustness in the field.

Keywords: Sepsis scores, infections, child deaths, infant mortality, primary health

1. Introduction

Although infection is one of the leading causes of death among children in developing countries [1], there remains a paucity of published studies on presentation and assessment in this scenario. Sepsis is the systemic response to infection [2]. According to the World Health Organization (WHO), the “big four” killers of children are severe pneumonia, diarrhea, malaria and measles [3]. WHO uses the term severe when children develop acidosis or hypotension [3]. Sepsis deaths

are most likely to be due to severe sepsis or septic shock [4]. An expert panel drawn from all over India has drawn guidelines for the diagnosis and management of sepsis and septic shock that are applicable to resource-limited environments [5]. They acknowledged several potential barriers to the adherence and implementation of guidelines in these settings. Lack of standard definitions, appropriate for such areas, increase the difficulties in patient triage, management and performance of epidemiological studies to guide public health interventions. Variability in case definition compounded by limited access to investigations, causes difficulty in making inter and intra-country comparisons. Widely prevalent malnutrition and human immunodeficiency virus (HIV) infection

*Corresponding author: Subhashchandra R. Daga, MIMER Medical College, Talegaon Dabhade 410507, India. Tel.: +91 02114 228532; Fax: +91 02114 223916; E-mail: subhashdaga@yahoo.com.

also influence the presentation and management strategy. The International Pediatric Sepsis Consensus Conference (IPSCC) definitions [6] need to be modified for such areas because low staffing levels, limited equipment and laboratory backup along the referral pathways mean that gaining accurate detailed information on the various parameters may be problematic. For resource poor areas, sepsis-grading systems based mainly on clinical parameters are best suited. We constructed category definitions using information, which would be accessible in our setting, building on the work of the IPSCC [6] and a review of pediatric sepsis definitions by Brilli and Goldstein [7]. We then assessed the modified score against the IPSCC score to see how many patients fit into each category. Thus, we aimed to establish the feasibility and utility of simpler definitions and use this information to suggest further modifications.

2. Materials and methods

2.1. Population

The sample comprised all critically sick children admitted consecutively to a pediatric intensive care unit (PICU) in a pediatric referral centre. It is located at a public hospital in a large city of a developing country. The state government fully funds the hospital, which in turn heavily subsidizes the services to the public. The patient populations are largely from the lower socio-economic group with referrals from urban, peri-urban and rural areas. The hospital is a regional centre for anti-retroviral therapy. Available treatments at the centre included antibiotic therapy, oxygen administration, enteral feeding and intravenous administration of fluids and medications. Short-term respiratory support was possible using bag and mask ventilation. The hospital authorities approved this study as part of the departmental audit program. They also waved the need for consent since we performed no tests or procedures specifically for this study. We received no external funding.

2.2. Data collection

We conducted the study during monsoon months of August and September 2006. Our impression is that a higher number of patients with infective illnesses are admitted during these months. Timing needed to fit in with department audit program and availability of

resident staff to collect the data (MA, SKJ, SBJ). We used a proforma to describe the following: demographic information, which included source of referral, clinical history, general and systemic examination findings, treatment data, discharge diagnosis and outcome. Examination findings were those at first contact to the medical team. The examination was conducted by one of the resident doctors (MA, SKJ, SBJ) representing three units of the pediatric department. All children received full blood count (FBC), blood culture and venous blood gas analysis. Patients with respiratory symptoms underwent chest x-ray examination. We considered a diagnosis of sepsis if there was fever or history of fever, chest indrawing, shock [8], decreased conscious level or a convulsion. Further tests were dependant on the clinical picture and decisions of the attending clinician.

2.3. Outcome measures

We categorized the sample using the IPSCC criteria and the Sassoon General Hospital (SGH) criteria, adapted from IPSCC [6] (Table 1). The adapted criteria were created based on data usually available to the team at presentation. The subjects were sub-grouped as having acute (with no co morbidity) or acute-on-chronic illness (with a co morbidity). The numbers in each category from the SGH criteria group and IPSCC criteria group were compared to see if there were any differences between the two in using the adapted system. Data were collected on clinical outcome, which was defined as survival to discharge or death. Since the data was of a descriptive nature, formal statistical tests were considered unnecessary.

3. Results

We studied one hundred consecutive admissions with no exclusions and data were available for all parameters. Tables 2 and 3 show demographic data, presenting features, investigations and outcome. Forty-nine patients were less than six months of age and 51 were male. Seventy-four patients presented at our hospital first and 26 patients were referred from other health facilities. Eighty patients were diagnosed to have acute illness while 20 had acute-on-chronic illness. All patients with clinical signs of shock had acidosis. Thirty-eight patients had either convulsions or altered conscious level or both. FBCs were indicative of sepsis [9] in 57 patients and 34 patients had bacterial growth on blood culture.

Table 1
Definitions of sepsis from Sassoon General Hospital and International Pediatric Sepsis Consensus Criteria

Sepsis category	Sassoon General Hospital	International Pediatric Sepsis Consensus Conference
Systemic immune response syndrome	Presence of at least two of the following, one of which must be abnormal temperature or leukocyte count: Core temperature °C > 38.5 °C or < 36.5* Abnormal full blood count** Tachypnea or tachycardia*	Presence of at least 2 of the following four criteria, one of which must be abnormal temperature or leukocyte count: 1. Temperature °C > 38.5 °C or < 36 °C 2. Heart rate > 2 SD above normal for age or for children < 1-year-old: bradycardia, defined as HR < 10th percentile for age 3. Respiratory rate > 2 SD above normal for age or mechanical ventilation 4. White blood cell count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or > 10% immature neutrophils
Sepsis	Systemic immune response syndrome and pH < 7.3 and altered mental status/chest indrawing	Systemic immune response syndrome in the presence of or as a result of suspected or proven infection
Severe sepsis/Septic shock	Sepsis + clinical signs of shock by assessment of peripheral perfusion and/or no urine passed for 12 h	Sepsis + one of the following: 1. Acute respiratory distress syndrome 2. Two or more other organ dysfunctions 3. Cardiovascular organ dysfunction defined as: despite administration of isotonic intravenous fluid bolus ≥ 40 mL/kg/h Hypotension blood pressure < 5th percentile for age or systolic blood pressure < 2 SD below normal for age or Need for vasoactive drug to maintain blood pressure in normal range (dopamine > 5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) or Two of the following: 1. Unexplained metabolic acidosis: base deficit > 5.0 mEq/L 2. Increased arterial lactate > two times upper limit of normal 3. Oliguria: urine output < 0.5 mL/kg/h 4. Prolonged capillary refill > 5 sec 5. Core to peripheral temperature gap > 3 °C
Organ dysfunction	Severe sepsis/septic shock + presence of recent altered organ dysfunction such as biochemical markers of abnormal liver*** or renal function****	Sepsis and organ dysfunction*****

*Core temperature > 38.5 °C < 36 °C, heart rate > 2 SD above normal for age, respiratory rate > 2 SD above normal for age (5).

**Leucocyte count elevated or depressed for age or > 10% immature neutrophils (9).

***No urine passed for 12 h (5).

****Total bilirubin > 4 mg/dL in patients outside the neonatal period (5).

*****Serum creatinine > 1 mg/dL (5).

The distribution of organisms grown was as follows: *Staphylococci* 10, *Escherichia coli* 6, *Candida* 5, *Pseudomonas* 3, *Klebsiella* 2, *Streptococcus* 1, *Trichosporia* 2, *Acinetobacter* 2, *Ralstonia* 1, *Brevundimonas* 1, and *Alcaligenes* 1.

Treatment included fluid resuscitation, inotrope infusion in presence of clinical shock (8) and/or

a venous pH < 7.3, antibiotics, oxygen administration, enteral feeding after stabilization, and thermal protection. Table 4 compares the SGH and IPSCC sepsis categorization for the sample. There were 27 cases of no sepsis under SGH and 10 under IPSCC. The severer forms of sepsis such as severe sepsis, septic shock and those with organ dysfunction did not vary in the

Table 2
Demographic data, background illness and presenting features
of study population. (Subjects = 100)

Clinical feature	Frequency	Death (%) ¹
Demographic features		
Age (Months)		
Less than 6	49	22
6-12	23	26
13-60	20	20
More than 60	8	25
Sex		
Male	59	25
Female	41	20
Referral		
Direct admission	74	19
Referrals	26	34.6
Nutritional status		
Normal	33	15
Protein Energy Malnutrition	67	27
Protein Energy Malnutrition	53	22.6
Grade I & II		
Protein Energy Malnutrition	14	43
Grade III & IV		
Illness Category		
Acute Illness	80	24
Acute-on-Chronic Illness	20	20
Symptoms/Signs		
Fever	80	26
Tachycardia	78	23
Chest indrawing	72	22
Convulsion	21	24
Altered conscious level	17	35
Decreased urine output 2	5	40
Dehydration	9	44
Shock	19	42

Abbreviations- PEM- Protein Energy Malnutrition, Gd- Grade.

1. Percentage of sample with this variable who died.

2. Decreased urine output (5).

two groups. Overall mortality was 23%. Of the 20 admissions with acute-on-chronic illness, four died and of the 80 patients admitted with acute illness 19 died. Of the 23 deaths, ten children had presented primarily with symptoms of cold shock and nine young infants (less than two months of age) had respiratory distress at presentation. Nearly a third of subjects presenting with neurological symptoms died. Two patients with HIV infection died, one with tuberculous meningitis and one with *Escherichia coli* sepsis.

4. Discussion

IPSCC describes the pediatric sepsis continuum as including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and organ

dysfunction, depending upon clinical and laboratory parameters [6]. It is important that suitable sepsis categorization is available for the areas where most sepsis deaths occur to facilitate triage, for treatment and for generation of epidemiological data. We used a modified score and compared it with the IPSCC to support validity of the adapted scoring systems. We found the modified scoring system easy to use, with all data collected at presentation. We believe that using actual data on patient presentation, albeit with a small sample, is an original approach to the generation of sepsis scores and our experience with this could be useful to facilitate further development methods for sepsis scoring systems.

The profile of PICU admissions highlights the presence of predispositions such as young age, malnutrition and HIV infection. Presence of fever, FBCs suggestive of sepsis [9] and positive blood culture show that infection is common among PICU admissions. In terms of clinical findings, 72% of patients had chest indrawing. Of these, only 19 patients had radiographic evidence of pneumonia. Mortality rate was 22% in presence of chest indrawing. WHO guidelines suggest a diagnosis of severe pneumonia among children with chest indrawing when x-ray facilities are not available. Earlier we have shown that severe pneumonia and severe sepsis may be clinically indistinguishable [10] and the present study provides further supportive evidence. We believe that chest indrawing is useful in sepsis categorization, with or without presence of pneumonia, reflecting possible cardiac and respiratory dysfunction, and metabolic acidosis resulting from impaired tissue perfusion. Our findings support the concept that chest indrawing reflects severe forms of sepsis such as severe sepsis or septic shock. Thus, a clinical criterion such as chest indrawing is a useful indicator of severe sepsis at peripheral health facilities. Neurological dysfunction in form of altered conscious level with or without convulsion had a relatively high mortality, suggesting either decreased cerebral perfusion secondary to shock or a primary infection of central nervous system. We have recognized this finding by acknowledging it as a main indicator for severe sepsis in our suggested peripheral area categorization. With respect to laboratory findings, we have confirmed our previous findings that only a small proportion of acidosis was attributable to diarrhoea [10]. Therefore measurement of acidosis, where available, is an important supportive evidence in categorizing septic illness. Nearly 50% of patients with a pH less than 7.2 died. Taking into consideration the poor outcomes associated with chest indrawing,

Table 3
Investigation result and outcome (Subject = 100)...continued.

Investigation Frequency Death (%) ¹			Investigation Frequency Death (%)			Investigation Frequency Death (%)		
HIV infection			FBC consistent With sepsis(9)			Sepsis category		
Present	7	28.5	Yes	57	28	SIRS	32	6
Absent	93	22.6	No	43	16	Sepsis	23	21.7
Venous PH at admission			Lobar consolidation (Chest X ray)			Severe sepsis/Septic shock		
Less than 7	4	100	Present	19	16	Organ dysfunction	2	100
7 – 7.1	16	37.5	Absent	81	24.7	No sepsis	24	12.5
7.11 – 7.20	14	36	Blood culture			Outcome		
7.21 – 7.2	11	18	Positive	34	20.6	Discharged	77	
7.3 and more	55	11	Negative	66	24	Died	23	

Abbreviations- HIV- Human Immunodeficiency Virus, SIRS- Systemic Immune Response Syndrome.

1. Percentage of sample with this variable who died.

Table 4
Results compared by Sassoon General Hospital and International Pediatric Sepsis

Consensus Conference Category				
Sepsis category	Sassoon General Hospital	International Pediatric Sepsis Consensus Conference	Not diagnosed by Sassoon General Hospital	Not diagnosed by International Pediatric Sepsis Consensus Conference
SIRS	26	42	16	0
Sepsis	30	31	1	0
Severe sepsis	15	15	0	0
Organ dysfunction	2	2	0	0
No sepsis	27	10	0	17

Abbreviations- SIRS- Systemic Immune Response Syndrome.

neurological dysfunction and acidosis, our findings, like those of De Oliveira, suggest that it is not only children with clinical signs of severe shock according to the IPSCC definitions, who may require hemodynamic support [11]. Our study suggests that the use of simple clinical signs or laboratory evidence of acidosis, when available, may be important supportive evidence in the diagnosis of severe sepsis or septic shock and for hemodynamic support.

Overall mortality of our study sample, in absence of mechanical ventilation, was 23%. This is substantially lower than reported in a recent study where survivals decreased to 49% in children who did not have access to mechanical ventilation for 6 hours and more, and among historical controls from the same centre [12]. Published mortality rates in septic shock from other Indian hospitals are in the same range [12]. Exclusion of children less than 30 days, shock due to hypovolemia and severely malnourished children, in these samples, makes comparison with our patients difficult, but we

believe by not excluding these cases, we have studied a representative sample of children who may present at the receiving room of a hospital such as ours. In our study, clinical outcome could possibly have been different, in ten children with inadequate respiratory effort and one child with initial adequate effort who died within 12 hours of admission, if mechanically ventilated.

We used FBC to support the diagnosis of SIRS and as a proxy for microbial culture because of its easier availability and rapid turn around time. An abnormal FBC may give confidence to offer hemodynamic support when associated with early signs of impaired perfusion or in the presence of a low pH. We believe it is unrealistic to expect accurate repeated charting of temperature, respiratory and heart rates at a health facility in a developing country with a very unfavorable nurse to patient ratio. We however found that the SGH definitions under-diagnosed SIRS and over-diagnosed 'no sepsis' as compared to the IPSCC categorization. This was because IPSCC classification diagnoses SIRS by clinical

parameters alone whereas abnormal FBC was essential for its diagnosis under SGH categorization. FBC has limitations and early in sepsis, the FBC may be within normal limits. Therefore, we support the suggestion by Singhi et al. [5] that either abnormal temperature or abnormal leukocyte count may be adequate to categorize SIRS. We used this finding to suggest further modifications for peripheral health facilities. However, the SGH criteria did not miss any cases of severe sepsis or shock despite its simplicity of use. The SGH criteria also identify cases that need circulatory support immediately on admission. Like Brilli and Goldstein [7], we feel the precise delineation of severe sepsis as opposed to septic shock may be artificial as they may be stages of the same dynamic process. IPSCC defines septic shock as severe sepsis with cardiovascular dysfunction and finds definition of septic shock problematic, as children often maintain their blood pressure until they are severely ill and shock may occur long before hypotension occurs in children [6]. Severe sepsis/septic shock have cardiovascular and respiratory involvement in most cases. However, the degree of cardiovascular or respiratory involvement can be assessed only in a sophisticated set up. Besides, conventional parameters to diagnose cardiovascular dysfunction are not without problems. Blood pressure monitoring in developed world is not without problems [13] so is the case with capillary refill time [14]. Diagnosing organ dysfunction in the resource poor setting may be confined to liver and kidneys, where jaundice and reduced urine output may give a clue. Estimation of serum bilirubin and serum creatinine may not be very difficult.

Building on this work, we suggest that for resource poor areas of developing countries the utility of using only three categories should be assessed, with some criteria being desirable but not mandatory if unavailable or non supportive (Table 5). The three categories are early sepsis, sepsis and severe sepsis. Early sepsis,

an equivalent of SIRS, is diagnosed if there is a pyrexial illness and there is evidence of site infection. We believe that a history of fever, if the patient is between fever spikes at presentation, or assessment of skin temperature by touch, if there are difficulties in temperature measurement, will be acceptable in this setting. As with IPSCC guidelines, hypothermia is also considered significant especially in neonates, young infants and severely malnourished children. SIRS in presence of infection is sepsis. SIRS associated with conditions such as trauma, non-cardiac surgery or pancreatitis will have other clinical correlates, and is far less common for children in developing countries than bacterial infection. We feel that from the perspective of peripheral areas of developing countries, the distinction between SIRS and sepsis may be irrelevant at least at peripheral health facilities. To delineate severe sepsis, we have utilized our findings that both chest indrawing and altered mental state reflected severe disease, and have added these to other indicators of shock.

We believe these simplifications have the potential to be useful in primary care setting of low-resource regions, both for management and documentation. Timely recognition and treatment is known to modify the later disease course [15]. It is reasonable to expect that when both categories are suspected/detected at the point of presentation, an antimicrobial is administered and supportive therapy is instituted immediately.

In summary, we detailed the clinical profile of critically sick children admitted to an intensive care unit in a resource-poor setting, and fit the data to a modified definition of sepsis, relying on easily assessed clinical features, FBC and blood gas analysis, where possible. We assessed the modified score against the IPSCC score to see how many patients fit into each category. Examining the performance of the simpler classification

Table 5
Suggested categories of sepsis for use in peripheral areas

Category	Required criteria	Desirable criteria If available
Early sepsis	Any two criteria of; Hyper/hypothermia or H/O fever or Feels warm/feels cold Tachycardia Tachypnea	FBC
Sepsis	Early sepsis + Persistent chest indrawing	Chest x-ray normal in the presence of chest indrawing, or abnormal in the presence of pneumonia and low pH
Severe sepsis	Features of sepsis + One of the following; Weak pulses Cool/cold peripheries Mottling of skin Altered conscious level Decreased urine output for 12 hours Jaundice	

Abbreviations- FBC- Full blood count, H/O- History of.

paved the way for suggestions regarding further adaptations towards ease of use. We feel that a study to assess the performance of simpler scoring systems for sepsis definition in resource poor environments in both peripheral areas and the onward referral centers would be the next step forward in this process.

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