Point of care lactate for differentiating septic shock from hypovolemic shock in non-ICU settings: a prospective observational study

Lubaba Shahrin,[a,b,*] Monira Sarmin,[a,b] Irin Parvin,[b] Md. Maksud Al Hasan,[b] Mst. Arifun Nahar,[b] Abu Sadat Mohammad Sayeem Bin Shahid,[b] Shamsun Nahar Shaima,[b] Gazi Md. Salahuddin Mamun,[c] Shajeda Nasrin,[b] Tahmeed Ahmed,[a,b,d] and Mohammod Jobayer Chisti[a,b]

[a]Clinical and Diagnostic Services, icddr,b, Dhaka, Bangladesh
[b]Nutrition Research Division, icddr,b, Dhaka, Bangladesh
[c]Infectious Diseases Division, icddr,b, Dhaka, Bangladesh
[d]Office of Executive Director, icddr,b, Dhaka, Bangladesh

The Lancet Regional Health - Southeast Asia 2024;30: 100500

Published Online xxx
https://doi.org/10.1016/j.lansea.2024.100500

Summary

Background Septic shock and hypovolemic shock are life-threatening illnesses that necessitate immediate recognition and intervention, as they can result in deadly consequences. While the underlying processes may vary, both entities can exhibit hypotension and organ dysfunction. No studies have been conducted on bedside testing to differentiate between these illnesses. Lactate measurement has been established as a viable option for early detection of septic shock. However, its role in diagnosing hypovolemic shock has yet to be evaluated. The aim of the study was to investigate alterations in lactate levels among diarrheal patients with septic shock and hypovolemic shock following the administration of first fluid resuscitation.

Methods We conducted a prospective observational study in critically ill diarrheal adults aged ≥18 years in the emergency ward in Dhaka Hospital of icddr,b from 21st October 2021 to 31st May 2023 (total 19 months). The enrollment process was operational between 8:30 AM and 5:00 PM. Diarrheal adults with a diagnosis of sepsis with shock featured with poor peripheral perfusion (characterized by cold periphery and weak or absent pulse and capillary refill time >3 s) or hypotension (characterized by mean arterial pressure <65 mm-Hg) were enrolled as cases and consecutive diarrheal patients without any obvious features of sepsis with hypovolemic shock (due to severe dehydration) comprised the comparison group. POC lactate test was done at hours 0, 1st and 6th by StatStrip Lactate meters (Nova Biomedical, US) to all enrolled patients. For comparison of POC lactate levels, we used paired t-test for comparing the lactate samples drawn at hour 0, hour 1 and 6 with the septic shock and hypovolemic shock group. Odds ratio (OR) and their 95% confidence intervals (CIs) were used to demonstrate the strength of association. The study was registered at Clinicaltrials.gov (NCT05108467) and received institutional ethical approval (PR-21097).

Findings Of 435 patients, 135 had septic shock and 141 had hypovolemic shock, rest 41 patient responded with fluid bolus. 25% (34/135) of the people in the septic shock group died whereas there is no mortality in the hypovolemic shock group. The number of patients visiting from outside Dhaka city had more septic shock than from inside were higher in comparison with (55% vs. 28%; $p < 0.001$). Statistically significant difference was observed between septic shock and hypovolemic shock group for a median POC lactate in 0, 1st and 6th hours with an OR of 1.07 (95% CI: 0.99, 1.17; $p = 0.039$); 1.48, (95% CI: 1.28, 1.70; $p < 0.001$) and 2.36 (95% CI: 1.85, 3.00; $p < 0.001$), respectively. The gradient of 1st to 2nd sample between septic shock and hypovolemic shock was found to be significantly different (OR: 0.74, 95% CI: 0.64, 0.85; $p < 0.001$).

Interpretation POC lactate test can detect septic shock by differentiating hypovolemic shock in diarrheal patients. By providing quick, reliable and accurate result this test can help clinicians quickly diagnose and treat time-sensitive condition, like septic shock.

Funding The study was funded by Global Affairs of Canada (GR-01726). The donors had no role in the design, implementation, analysis, data interpretation or writing manuscript, or decision to publish. The corresponding author had access to all data and takes responsibility for the final approval and submission of the manuscript.

*Corresponding author. icddr,b, 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka, 1212, Bangladesh.
E-mail address: lubabashahrin@icddrb.org (L. Shahrin).

Keywords: Adults; Diarrhea; Hypovolemic shock; Point of care lactate test; Mortality (case fatality); Septic shock

Research in context

Evidence before this study

Our comprehensive search on PubMed and Web of Science, encompassed publications from resource-limited contexts in English from January 1, 2000, to June 30, 2021. To identify relevant research regarding the role of lactate in septic shock in diarrheal patients, we used the keywords ("Lactate" OR "Serum Lactate" OR "Plasma Lactate") AND ("Septic shock" OR "Sepsis" OR "Septicemia" OR "Septicaemia") AND ("Adult" OR "Age ≥18 years") AND ("Diarrhea" OR "Acute watery diarrhea" OR "Severe diarrhea" OR "Diarrheal diseases"). We also conducted a systematic search using the keywords ("Lactate" OR "Serum Lactate" OR "Plasma Lactate") AND ("hypovolemic shock" OR "severe dehydration" OR "Hypovolemia" AND ("Adult" OR "Age ≥18 years") AND ("Diarrhea" OR "Acute watery diarrhea" OR "Severe diarrhea" OR "Diarrheal diseases"). Multiple studies have documented the significance of serum lactate or plasma lactate in diagnosing septic shock and using lactate-guided fluid bolus in intensive care units. Nevertheless, there is a lack of data on the use of lactate in septic shock patients with diarrhea or diarrheal patients diagnosed with septic shock in diarrheal settings by lactate. We conducted additional research on papers that report serum or plasma lactate levels in cases of acute dehydration and the subsequent changes observed with rapid rehydration through intravenous fluid administration. Our investigation revealed a need for more research in this area and highlighted a gap in the study of the role of lactate in hypovolemic dehydration.

Added value of this study

Our research demonstrates the notable efficacy of point of care lactate testing in distinguishing between fluid-unresponsive septic shock in people with diarrheal disease and hypovolemic shock caused by severe dehydration. Our study is the first to examine blood lactate levels in adult patients with diarrhea. We focused on identifying the key distinctions between fluid-responsive hypovolemic shock and fluid-unresponsive septic shock. This differentiation is vital in reducing the hazards linked to unwarranted volume substitution in individuals who do not respond to hydration. The results of our study show that point of care (POC) blood lactate measurement has the ability to distinguish between septic and hypovolemic shock, providing a useful method for early identification. Early detection of septic shock with point of care lactate tests enables critical care clinicians, particularly in the emergency room, to promptly and effectively intervene in the treatment of very ill patients experiencing diarrhea and low blood pressure. In situations with low resources, where there is a high prevalence of diarrheal disorders, this method can greatly enhance patient outcomes by optimizing fluid management and minimizing the negative effects of incorrect treatments.

Implications of all the available evidence

In diarrheal settings, septic shock presents a significant mortality risk. Due to its overlapping clinical characteristics with hypovolemic shock, immediate detection and care are necessary to prevent the deadly effects of multi-organ dysfunction. The results of this study concerning the use of point of care lactate testing at admission and subsequent change in lactate gradient after the initial hour of fluid administration have the potential to greatly enhance the treatment of septic shock and decrease mortality rates in low-middle income countries.

Introduction

In high diarrhea burden settings, diarrheal infections can be life-threatening if hypovolemic shock due to severe dehydration and septic shock cannot be distinguished quickly.[1] Vibrio cholerae, ETEC, Rotavirus, and Shigella cause acute watery diarrhea in adults in developing countries.[2] These organisms can enter the bloodstream and generate malregulated immune responses that cause sepsis, septic shock, and irreparable organ damage.[3,4] Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.[5,6] The Sepsis-3 criteria by Third International Consensus Definition for septic shock identify septic shock patients having persistent hypotension and serum lactate level >2 mmol/L.[7] However, clinical features like altered mentation, hypoperfusion and hypotension are overlapping with the features of hypovolemic shock due to severe dehydration make the diagnosis of septic shock difficult[8] in settings with high diarrhea prevalence.

Global burden of sepsis is more than 31.5 million every year with an estimated 5.3 million deaths.[9] Approximately 85% of sepsis cases and sepsis-related deaths worldwide occurred in developing countries.[9,10] Report from the largest database on diarrheal disease in the world, belonged to the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), 69% of diarrheal adults progressed to septic shock from severe sepsis.[11] Without timely identification and intervention, septic shock may proceed to organ failure and death.[12]

Widespread tissue hypoperfusion in the body triggered anaerobic metabolism and overproduction of lactate as a by-product. Besides persisting hypotension with a mean arterial pressure of below 65 mm-Hg, blood lactate over 2 mmol/L is current recommended indicator of septic shock.[5,13] There are paucity of literature describing the temporal relation of lactate with dehydration and their similarity or dissimilarity with septic shock. Based on this important aspect, our study objective was to explore the changes in point of care (POC) lactate levels in adult diarrheal patients with septic shock and hypovolemic shock after initial fluid resuscitation and thus differentiating them from septic shock and hypovolemic shock.

Methods

Study site & settings

The study was conducted in Dhaka Hospital of icddr,b, which serves over 200,000 diarrheal patients free of cost every year.[14] Being a free of cost hospital, the vast majority of the patients come from poor socioeconomic backgrounds. Patients residing in the peri-urban area of Dhaka frequently seek treatment for diarrhea at this facility due to convenient communication. The hospital usually experiences two seasonal peaks of patients every year. During a large diarrheal epidemic in 2018, this hospital had saved between an estimated 12,523 and 17,265 lives.[14] Although this is a diarrheal hospital, patients often come with other associated illnesses, like pneumonia, malnutrition, sepsis, septic shock and electrolyte imbalances and also with comorbidities like diabetes, hypertension, cardiovascular diseases, asthma, malignancy. The hospital has dedicated doctors, nurses, and support staff who engage in patient service from entry to discharge. Soon after admission, the hospital triage nurses obtain a brief medical history and quickly assess the patients, focusing on the severity and complexity of their diarrhea and dehydration and other health problems. Thereafter, emergency physician reassesses them and triage them and starts resuscitation if required or send them to appropriate words like general ward or intensive care unit (ICU). Patients are transferred to the ICU if deemed necessary with presence of septic shock, impaired consciousness, convulsion, severe pneumonia with hypoxaemia, respiratory failure, or require cardio-pulmonary resuscitation. More details of the activity in the study site have been described elsewhere.[11]

Study design and participants

We conducted a prospective observational study in critically ill diarrheal adults aged ≥18 years in the emergency ward in Dhaka Hospital of icddr,b from 21st October 2021 to 31st May 2023 (total 19 months). The enrollment process was operational between 8:30 AM and 5:00 PM. Diarrheal adults with a diagnosis of sepsis with shock featured with poor peripheral perfusion (characterized by cold periphery and weak or absent pulse and capillary refill time >3 s) or hypotension (characterized by mean arterial pressure <65 mm-Hg)[5] were enrolled as cases and consecutive age and sex matched diarrheal patients with hypovolemic shock (due to severe dehydration) but without any obvious features of sepsis comprised the comparison group [Fig. 1].

The entry point for admission to the hospital is acute watery diarrhea defined by loose or watery stool ≥3 times over 24 h period.[8] Patients presenting with severe dehydration assessed by the admitting doctor were enrolled as a comparison control group. Patients having emergency condition that might require urgent referral within an hour of admission, malignancy and on chemotherapy or radiotherapy, or life-threatening conditions requiring cardiopulmonary resuscitation on arrival were excluded from the study.

Procedures

Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[5] was followed to identify clinical sepsis, by the presence of signs and symptoms of both inflammation and infection. Key clinical features include hyperthermia (temp >38.5 °C) or hypothermia (temp <35 °C), tachycardia, plus either bounding pulses or, altered mental status or, hypoxemia in the absence of pneumonia or, abnormal WBC count (>12,000 x 10^9/L or <4 x 10^9/L) or band and neutrophil ratio ≥0.1) or, increased serum lactate level >2 mmol/L.[5,6]

If sepsis induced hypotension (MAP<65 mm Hg in adults) was persisting despite adequate fluid resuscitation, or having a serum lactate level greater than 2 mmol/L persisting after fluid resuscitation, the condition was defined as septic shock.[6] Severe dehydration was defined as presence of at least two of the following signs: i) general appearance (lethargy or unconscious), ii) skin pinch (goes back very slowly), iii) sunken eyes, iv) thirst (unable to drink or drink poorly), and vi) radial pulse (absent or uncountable).[15,16]

Point of care lactate measurement was performed at hour 0 (baseline), 1st hour and 6th hour using venous blood with handheld device named "StatStrip" lactate from nova biomedicals.[17] The detection range was 0.7–20.0 mmol/L and a result turnover time was 13 s. This POC device requires 0.6 micro/litres of whole blood/capillary blood. The device uses single-use test strips containing an enzyme-coated electrode. A 12-h routine calibration was carried out for quality assurance. This is a handheld device designed for measuring lactate levels in whole blood, serum, and plasma.[18] The supplier did not participate in any research activity except providing the device. We evaluated lactate for 20% of study participant to compare with the POC lactate and to validate the POC lactate device we are using in our study population (Supplementary Table S1).

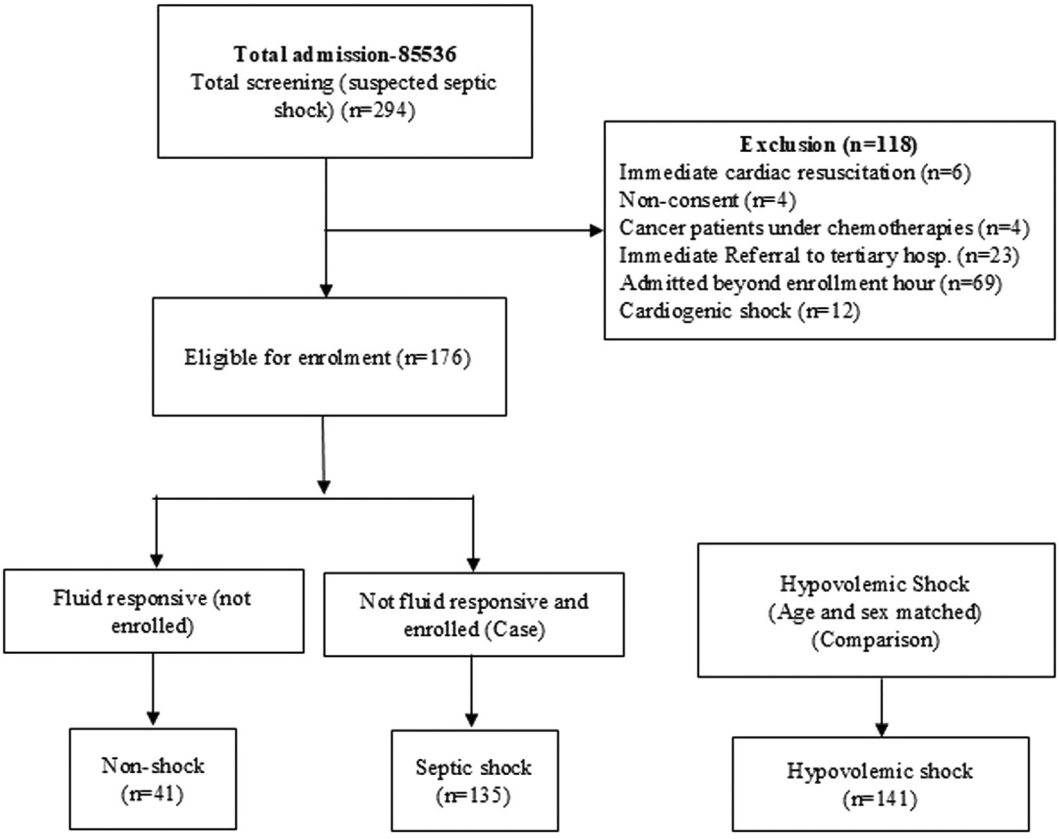


Fig. 1: Point of care (POC) lactate study profile showing participant enrollment.

Correction of dehydration was done following hospital protocol.[16] Patients diagnosed as septic shock has been immediately shifted to the ICU for appropriate resuscitation, which included broad-spectrum antibiotic therapy, intravenous fluids, inotropes, oxygen therapy, frequent monitoring, and nutritional support. Mechanical ventilation was used for the management of those with respiratory failure. After quick ICU resuscitation, the on-duty physician assessed all the patients, including taking the medical history and thorough clinical examinations.[11] Arterial oxygen saturation (SpO_2) was measured using a portable pulse oximeter (Handheld Vital Signs Monitors - NT1D, Solaris medical technology, Inc., USA), and blood glucose was estimated using bedside Accu Chek Active (Roche Diagnostics GmbH, Mannheim, Germany). Those with hypoxaemia received O_2 supplementation through a nasal cannula (if requirement of oxygen was up to 5 L/min) or face mask (requiring oxygen from 6 to 9 L/min) or non-rebreather mask (for those who required ≥10–15 L/min). Appropriate broad-spectrum antibiotics (IV third-generation cephalosporins plus gentamicin) and metronidazole were administered within 1st hour of admission. Appropriate feeding (nothing by mouth with maintenance fluid for patients with septic shock) was provided as and when required. The goal was to achieve good peripheral perfusion with a MAP of ≥65 mm Hg and/or urine output >0.5 ml/kg/hour. The amount of stool output was closely monitored upon arrival and afterward and matched with iv or oral fluid, as appropriate.[11]

For routine patient care, a complete blood count, serum electrolyte, serum creatinine, C-reactive protein, blood C/S, random blood sugar, and other relevant investigations according to clinical requirement were sent. A chest radiogram was done using a mobile X-ray machine for suspected pneumonia.

Statistical methods

Sample size: There was a lack of published research on the lactate levels in patients having hypovolemic shock and the subsequent changes of these levels over a period of time. Hence, it is necessary to do a posthoc analysis to determine the trial's statistical power after 18 months of patient enrolment. In the posthoc analysis, we focused on the median difference of POC lactate levels between the septic shock group (0.55) and the hypovolemic shock group (1.55) at time points 0 h and 1st hour, respectively. The calculated sample size of 251 participants

(117 with septic shock and 134 with hypovolemic shock) was determined. This sample size was enrolled over a period of one and a half years and provides a power of above 90%, which is considered sufficient for this research. Ultimately, prior to obtaining approval to discontinue the enrollment process from the Institutional Review Board, an additional 25 patients had already been enrolled.

Data entry, cleaning and data management were done in SPSS (Statistical Package for the Social Sciences-version 20.0 Windows) (SPSS, Chicago, IL). Statistical analysis was performed in STATA (Stata Statistical Software: Release 15, College Station, Texas 77,845, USA: Stata Corp LLC). Normally distributed continuous variables were presented by means, standard deviations, and skewed continuous variables were reported as median and interquartile range. The normality of the continuous variables were tested by histogram, Quantile–Quantile plot, and boxplot. Then, we did the Shapiro–Wilk test. Categorical variables were reported by frequencies and percentages. The chi-square test was used to compare the socio-biological, clinical, and laboratory parameters among patients with septic shock and hypovolemic shock. To identify the strength of the association of high lactate levels with septic shock in diarrheal adults, initially, a simple logistic regression model was built, and then a multiple logistic regression analysis model identified factors independently associated with septic shock after controlling for the relevant confounding variables. The odds ratio (OR) and their 95% confidence intervals (CIs) were used to demonstrate the strength of the association. We performed the Mann–Whitney U test for this nonparametric statistical data analysis to determine the difference between the two independent groups. For statistically significant, a p value was set <0.05. For outcome, septic shock and hypovolemic shock in socio–biological parameter adjusted variables were age, sex, resident, housing condition, and monthly family income (BDT); for clinical parameter adjusted variables were acute watery diarrhea, fever, cough, respiratory distress, hypertension, and diabetes mellitus; and for laboratory parameter adjusted variables were hemoglobin, hematocrit, total WBC count, different leucocyte count, platelet, C-reactive protein and serum creatinine. For visualization of some statistical analysis we used bar chart, line graph and receiver operating characteristics (ROC) curve. We did receiver operating characteristics (ROC) curve analysis with sensitivity and specificity tests to find the cut-off value of the maiden POC lactate which could determine the requirement of inotrope after fluid bolus with a given certainty.

Ethical considerations

The study received ethical approval from the Institutional Review Board of icddr,b (PR-21097, version 3.0, dated 04-10-2021). The study was registered at the NIH clinical trial registry on 17-11-2021 (NCT05108467). Before enrollment into the study, written informed consent was obtained from the participants. Participation was voluntary, and non-participation did not hamper the standard hospital management. The informed consent was translated in the local language for understanding.

Role of funding source

This project has been organized by icddr,b in cooperation with the development partners and the Government of the People's Republic of Bangladesh. Global Affairs Canada granted funding for this entire study (GR-01686). Funders had no role in study design, data collection, data analysis, interpretation, writing of the report.

Results

During the 19 months of the study period a total of 85,536 patients over 18 years were admitted with acute watery diarrhea. We screened 294 patients, of whom, 176 patients were eligible. Among them, 41 patients showed restoration of MAP after administering the bolus fluid and no longer qualified as septic shock. Finally, 135 patients comprised the septic shock group, and consecutively, 141 patients were enrolled in the hypovolemic shock group for comparison. In the septic shock group 25% (34/135) of the patient died, whereas patients with hypovolemic shock (0/141) were all discharged alive. Fig. 1 illustrated the enrollment pathway from screening to development of septic shock. The exclusion criteria from the screened 294 patients were listed in the Supplementary Table S2.

During the study period, 294 adult diarrheal patients with sepsis and septic shock were admitted to the Dhaka Hospital. Among them, 69 patients were admitted during the night shift. Due to resource constraints, the study team only followed those suspected patients admitted during the day shift from 8 AM to 5 PM. We excluded 49 patients (required urgent referral 23, known case of cancer or on chemotherapy 4, require cardiopulmonary resuscitation 6, cardiogenic shock 12 and no consent 4) and finally followed 176 patients for their clinical outcome. Among these 225 patients, 135 were finally labeled as septic shock, and we included them in this analysis as cases. The remaining 41 patients' blood pressure was restored by fluid bolus and did not qualify the criteria of septic shock, they were exempted from the analysis.

We also enrolled age and sex-matched 141 patients of hypovolemic shock during the study period and included them as control.

The demographic characteristics of the study participants revealed (Table 1) that patients with septic shock were older than patients having hypovolemic shock (47.1 years vs. 44.6 years). Females had more preponderance of septic shock, n = 72 (53.3%) and males had

Background characteristics	Septic shock; n = 135 (%)	Hypovolemic shock; n = 141 (%)	p value	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)
Age (Mean ± SD)	47.13 ± 15.08	44.64 ± 13.98	0.156	1.01 (0.99–1.03)	0.282	1.01 (0.99–1.03)
Sex						
Male	63 (46.67)	76 (53.90)		Reference		Reference
Female	72 (53.33)	65 (46.10)	0.230	1.34 (0.83–2.14)	0.947	1.02 (0.61–1.70)
Resident						
Inside Dhaka City	70 (51.85)	94 (66.67)		Reference		Reference
Outside Dhaka City	65 (48.15)	47 (33.33)	**0.013**	1.86 (1.14–3.02)	0.238	1.38 (0.81–2.34)
Housing condition						
Shared urban house or slum	90 (66.67)	124 (87.94)		Reference		Reference
Separate urban or village settlement	45 (33.33)	17 (12.06)	**0.000**	3.65 (1.96–6.78)	**0.001**	2.98 (1.53–5.81)
Monthly family income (BDT)						
≤12,000	49 (36.30)	76 (53.90)		Reference		Reference
>12,000	86 (63.70)	65 (46.10)	**0.003**	2.05 (1.27–3.32)	**0.013**	1.90 (1.15–3.14)

The bolded figures represents statistical significance of <0.05 p value.

Table 1: **Socio-biological characteristics of adults with septic shock and hypovolemic shock.**

more hypovolemic shock, n = 76 (53.9%). When the living arrangement is compared among the patients, shared urban or village settlement were two times odds of developing septic shock than those lived in shared urban house or slum (Table 1). Patients from wealthy household were more likely to have septic shock compared to those belongs to less wealthy family (Table 1).

Frequency of acute watery diarrhea was 123 (91%) and 141 (100%) in septic shock and hypovolemic shock group, respectively (Table 2). Patients from hypovolemic shock experienced more vomiting than those with septic shock (98% vs. 83%, p = 0.001). In the multivariate analysis, presence of cough and diabetes mellitus were significantly associated with septic shock compared to hypovolemic shock (Table 2). Patients with hypovolemic shock had higher hemoglobin; total WBC count; and platelet counts compared to the patients with septic shock (Table 3). Compared to the hypovolemic shock, patients with septic shock had significantly higher band-neutrophil (%) and C-reactive protein. Patients in septic shock group had significantly higher creatinine compared to patients in hypovolemic shock group (Tables 3 and 4).

In Fig. 2, two-line graphs portrayed the level of POC lactate in septic shock and hypovolemic shock at three different time point with their temporal trend. At enrolment (0 Hour), median (IQR) POC Lactate was 5.2 (3.7, 7.2) mmol/L and 4.5 (3.3, 6.9) mmol/L in septic shock group and hypovolemic shock group respectively and the difference was statistically significant (p = 0.039).

The significant difference also persisted for 1st hour [median (IQR) POC Lactate was 4.6 (3.4, 6.1) m moL/l and 3.0 (2.2, 4.3) mmol/L in septic shock group and hypovolemic shock group respectively, p < 0.001] and 6th hour [median (IQR) POC Lactate was 4.0 (2.9, 6.3) mmol/L and 2.1 (1.4, 3.1) mmol/L in septic shock group and hypovolemic shock group respectively, p < 0.001] (Fig. 2).

The Fig. 3 is a composite bar graph where the gradient of median value of POC lactate in two adjacent time points were shown. For example, the red bar

Associated conditions at enrollment	Septic shock; n = 135 (%)	Hypovolemic shock; n = 141 (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Acute watery diarrhoea	123 (91.11)	141 (100)	–	–	–	–
Vomiting	112 (82.96)	138 (97.87)	0.11 (0.03–0.36)	**0.000**	0.11 (0.03–0.40)	**0.001**
Fever	123 (91.11)	0 (0)	–	–	–	–
Cough	11 (8.15)	1 (0.71)	12.42 (1.58–97.57)	**0.017**	11.37 (1.40–92.19)	**0.023**
Respiratory distress	16 (11.85)	0 (0)	–	–	–	–
Hypertension	22 (16.30)	9 (6.38)	2.86 (1.26–6.45)	**0.012**	2.05 (0.82–5.12)	0.124
Diabetes mellitus	23 (17.04)	8 (5.67)	3.41 (1.47–7.93)	**0.004**	2.55 (1.00–6.48)	**0.050**

The bolded figures represents statistical significance of <0.05 p value.

Table 2: **Clinical conditions of the study participants at enrollment.**

Lab reports	Total count (n = 276)	Septic shock; n = 135	Hypovolemic shock; n = 141	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Hemoglobin level (Mean ± SD) (gm/dl)	273	12.25 ± 2.30	14.24 ± 2.18	0.67 (0.59–0.76)	**0.000**	0.51 (0.12–2.12)	0.358
Hematocrit (%) (Mean ± SD)	273	37.74 ± 6.67	43.89 ± 6.38	0.86 (0.82–0.90)	**0.000**	1.21 (0.74–1.96)	0.447
Total WBC count; Median (IQR) ([a]10^9/L)	273	13.16 (8.55, 17.53)	16.88 (13.39, 19.98)	0.96 (0.92–0.99)	**0.013**	1.18 (1.03–1.35)	**0.018**
Different Leucocyte count							
Neutrophil (%) (Mean ± SD)	273	56.41 ± 17.49	81.46 ± 10.71	0.89 (0.87–0.91)	**0.000**	0.96 (0.87–1.07)	0.488
Lymphocyte (%); Median (IQR)	273	12.30 (8.0, 18.30)	5.90 (4.10, 8.05)	1.32 (1.23–1.43)	**0.000**	1.33 (1.06–1.67)	**0.014**
Band Neutrophil (%); Median (IQR)	273	23.0 (15.0, 30.0)	10 (6.0, 15.0)	1.12 (1.08–1.16)	**0.000**	1.02 (0.89–1.16)	0.781
Platelet; (Mean ± SD) ([a]10^9/L)	272	203.55 ± 75.92	307.61 ± 85.81	0.98 (0.98–0.99)	**0.000**	0.98 (0.97–0.99)	**0.004**
CRP; Median (IQR) (mg/dl)	237[a]	17.42 (11.77, 27.10)	0.98 (0.37, 2.26)	1.44 (1.31–1.59)	**0.000**	1.18 (1.05–1.33)	**0.004**
Serum creatinine; (Mean ± SD) (µmol/L)	274	266.31 ± 117.68	179.15 ± 77.96	1.01 (1.00–1.01)	**0.000**	1.00 (0.99–1.01)	0.780

The bolded figures represents statistical significance of <0.05 p value. [a]100 and 137 blood samples were tested for CRP from Septic shock group and hypovolemic shock group respectively. The rest were missed either for immediate referral or death.

Table 3: **Comparison of baseline laboratory parameters between patients with septic shock and with hypovolemic shock.**

Cutoff point	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+	LR−	Correctly classified (%)	PPV% (95% CI)	NPV% (95% CI)
3.8	75.56 (69.21–81.90)	46.34 (38.97–53.71)	1.39	0.55	67.84	82.26 (76.61–87.90)	36.54 (29.42–43.65)
3.9	74.81 (68.40–81.23)	53.66 (46.29–61.03)	**1.59**	**0.49**	**69.01**	84.17 (78.77–89.56)	39.29 (32.07–46.50)
4.0	71.11 (64.41–77.81)	53.66 (46.29–61.03)	1.51	0.56	66.08	83.48 (77.99–88.96)	36.07 (28.97–43.16)

The bolded figures represents statistical significance of <0.05 p value.

Table 4: **Cut off point of Point of lactate at enrolment require inotrope.**

(septic shock) of gradient I represented the median value of POC lactate done in hour 0 and hour 1 and similarly the blue bar (hypovolemic shock) of gradient I represented the median value of POC lactate done in hour 0 and hour 1. Both gradient I and II showed p value < 0.001 and gradient III is p = 0.022.

For septic shock group, difference between 1st and 2nd POC lactate was (5.1–4.6 = 0.5) 0.5 and for hypovolemic shock group, difference between 1st and 2nd POC lactate was (4.5–3.0 = 1.5) 1.5. Therefore, the calculated gradient was compared between septic shock and hypovolemic shock group and it revealed an OR: 0.74, 95% CI: 0.64, 0.85; p < 0.001. Similarly, the other two gradients were also statistically significant over subsequent time points. These changes indicated that POC lactate dropped more among the patients in hypovolemic shock group than among the patients in septic shock group and it was statistically significant.

Fig. 4 indicated that, POC lactate at enrolment had a predictive capacity of detecting inotrope requirement.

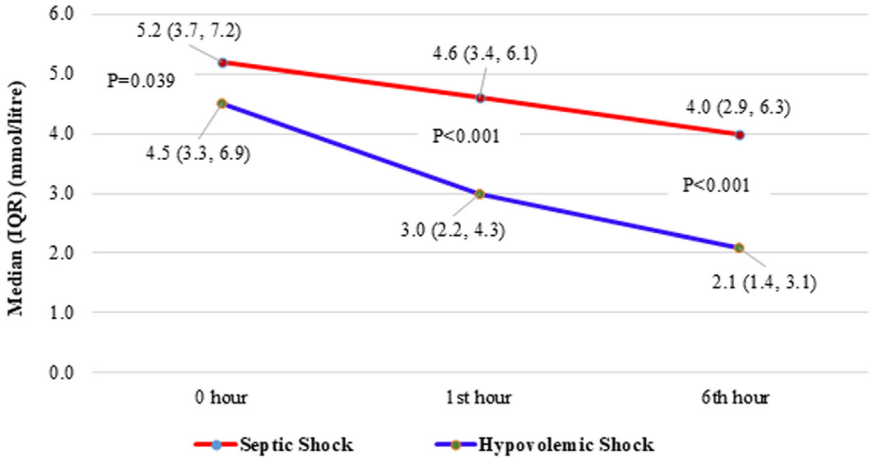


Fig. 2: Comparison of point of care (POC) lactate tests in 0 h, 1st hour and 6th hour between patients with septic shock and hypovolemic shock.

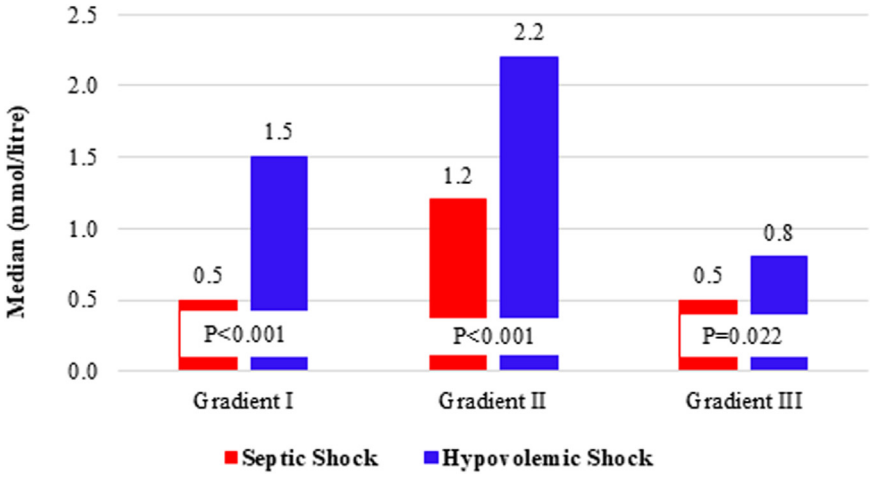
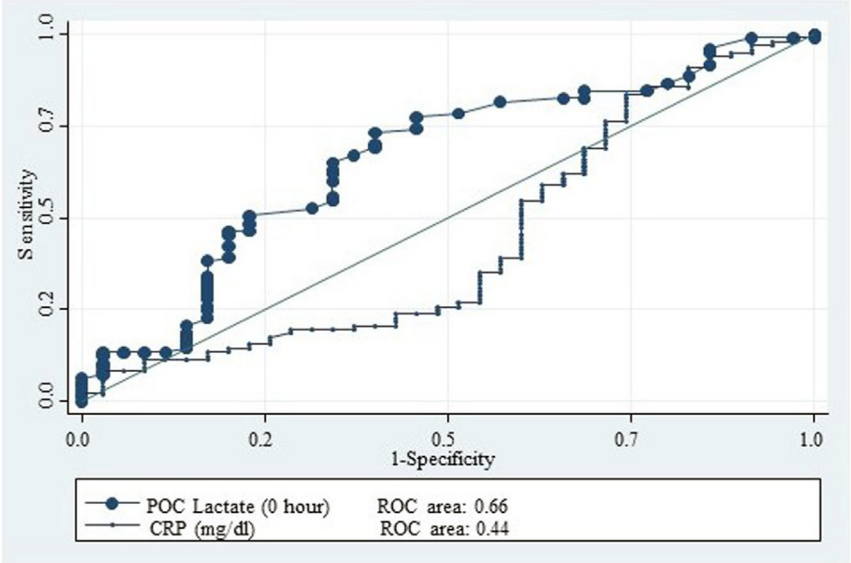


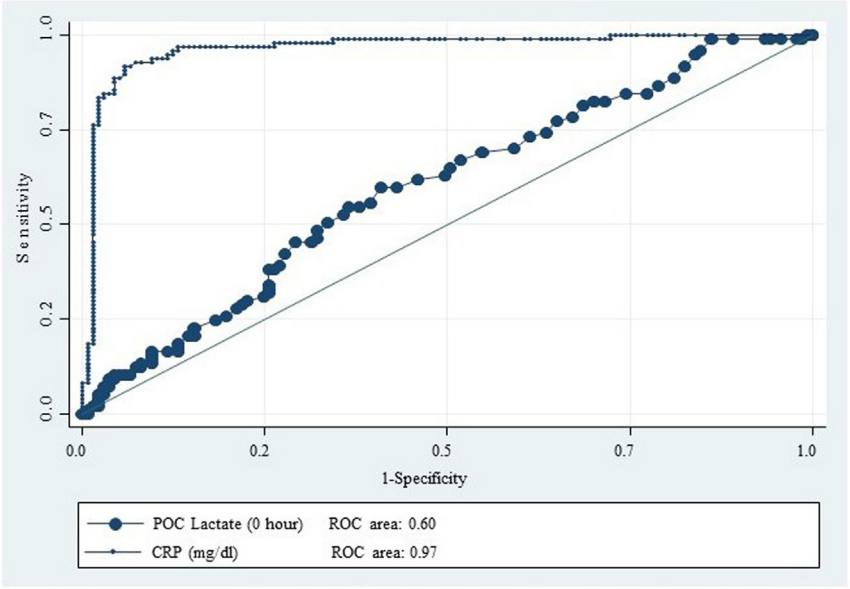
Fig. 3: Comparison of point of care (POC) lactate gradients at different time points between patients with septic shock and hypovolemic shock. **Gradient I: Red bar** and **Blue bar** correspond with difference of POC lactate values between 0 h and 1st hour in septic shock group and hypovolemic shock group respectively. **Gradient II: Red bar** and **Blue bar** correspond with difference of POC lactate values between 1st hour and 3rd hour in septic shock group and hypovolemic shock group respectively. **Gradient III: Red bar** and **Blue bar** correspond with difference of POC lactate values between 2 nd h and 3rd hour in septic shock group and hypovolemic shock group respectively.

The best cutoff point of POC lactate at enrollment was 3.9 mmol/L for requirement of inotrope with a sensitivity of 74.81% and specificity of 53.66% (Supplementary Table S3). The area under the receiver operating characteristics (ROC) curve was 66% (95% CI: 51.7–71.9). 0-hour POC lactate correctly classified 69% of cases with



Factors	Cut point	Area under region (AUR) (95% CI)	Sensitivity (%)	Specificity (%)	P value
Point of Care Lactate (0 hour)	3.9	0.66 (052-072)	74.81	53.66	**0.001**
CRP (mg/dl)	9.5	0.44 (0.32-0.56)	87.41	21.95	0.139

Fig. 4: Area under the Receiver Operating Characteristics (ROC) curve demonstrating the association of point of care (POC) lactate and C-reaction protein (CRP) with requirement of inotropes in septic shock at 0 h.



Factors	Cut point	Area under region (AUR) (95% CI)	Sensitivity (%)	Specificity (%)	P value
Point of Care Lactate (0 hour)	4.8	0.60 (0.50-0.64)	57.04 %	56.74 %	0.022
CRP (mg/dl)	5.4	0.97 (0.94-0.99)	94.07%	91.49%	0.000

Fig. 5: Area under the Receiver Operating Characteristics (ROC) curve demonstrating the association of point of care (POC) lactate and C-reaction protein (CRP) in 0 h between septic shock and hypovolemic shock.

a positive predictive value (PPV) 84.17% and negative predictive value (NPV) 39.29%. (Supplementary Table S3). Alternatively, the best cutoff point of C-reactive protein (CRP) at enrollment was 9.5 mg/dl for predicting the requirement of inotrope with a sensitivity of 87.41% and specificity of 21.95% (Supplementary Table S4). The area under the ROC curve was 44% which is not statistically significant (Fig. 4).

Fig. 5 showed the role of POC lactate and CRP in 0 h to detect septic shock or hypovolemic shock. The best cutoff point of POC lactate at enrollment was 4.8 mmol/L for predicting septic shock (sensitivity 57.04%; specificity 56.74%; $p = 0.022$). On the other hand, the best cutoff level of CRP at enrollment was 5.4 mg/dl for predicting the septic shock (sensitivity 94.07%; specificity 91.49%; $p < 0.0001$). The area under the ROC curve was 97% (95% CI: 94.0–99.0). Which is highly statistically significant (Fig. 5).

Discussion

To our knowledge, this is the first study on adults patients having diarrhea where we explored the differences in blood lactate between patients having fluid-responsive hypovolemic shock (hypovolemic) or and fluid-unresponsive septic shock.[19] In effort of minimizing the harmful effect of unnecessary volume replacement in fluid-unresponsive patients with diarrheal illness, our study demonstrates that point of care blood lactate tests that can differentiate septic shock from hypovolemic shock in diarrheal patients. Thus, early detection of septic shock by POC lactate tests would empower the critical care physicians, especially at Emergency department, to ignite appropriate care for the sickest patients having diarrhea and hypotension, in high diarrhea burden resource-limited settings.

Our study observed a high burden of septic shock among adults presenting with diarrhea and other co-morbid illness. A previous study from the same site reported that among 8863 adults with diarrhea and varying degrees of dehydration admitted into ICU, 240 developed septic shock.[11] Despite the adaptation of validated dehydration clinical assessment methods,[15] diarrheal patients presenting with a nonpalpable pulse, unrecordable blood pressure, and delayed capillary refill time often mislead emergency response physicians and they baffle to differentiate severe dehydration from severe sepsis or septic shock.[8]

This study showed a novel finding that POC lactate was equally elevated in severe dehydration and septic shock at the beginning of treatment. However, after initial fluid resuscitation it decreased to a greater degree in hypovolemic shock than in septic shock patients, thereby helping the clinician to continue fluid for the

hypovolemic shock patients though they might have several signs of sepsis and to follow sepsis bundle for patients having diarrhea and septic shock. Research indicated that the dehydration, diagnosed following WHO-defined assessment, is successfully managed following acute watery diarrhea in resource-limited settings, and no laboratory testing is required for uncomplicated diarrheal patients,[20] but the point of care lactate test has been proven to detect associated sepsis and septic shock in those settings that may help to avert fatal outcome.[11] Moreover, this test has been adopted to guide fluid therapy in critical care settings.[21,22] Although, our study is not designed to evaluate the mortality benefit of POC lactate test in diarhoeal adults, future intervention trial by introducing the POC lactate test in a high-diarrhea burden setting may contribute to reduce mortality by early identification and subsequent prompt treatment of septic shock.

Metabolic acidosis occurs in both severe dehydration and septic shock, expressed with intertwining clinical features, like abnormal mentation, tachycardia, tachypnea, hypotension, and poor peripheral perfusion.[11,19,20] Despite having protocolized recommendations for the management of both severe dehydration and septic shock, a quick bedside tool is essential for physicians' decision-making on rationalizing fluid therapy and the timely introduction of life-saving inotropes. In anaerobic conditions, blood lactate is elevated in both septic and hypovolemic shock. Prior to our study, we did not have any satisfactory tool to differentiate septic shock from hypovolemic shock derived from severe dehydrating diarrhoea such as in cholera or other cholera like illnesses. Importantly, our study resolved this issue as it revealed that after correction of severe dehydration, the lactate level rapidly decreases, in contrast with fluid bolus in septic shock, which is highly sensitive and specific.

We observed higher haemoglobin (Hb), total leucocyte count (TLC) and platelet (PLT) in patients having hypovolemic shock possibly due to hemoconcentration.[23] In acute diarrhea, due to losing water through stool and became hypovolemic, this hypovolemia causes hemoconcentration and in addition, blood cells those are staying near the endothelium come to the central circulation with an overall effect reflected as high Hb, TLC and platelet in hypovolemic shock. On the contrary, we observed more band neutrophil in septic shock group. Bands are immature neutrophil. To fight infection, initially the existing leucocyte come forward, however, when they are used up, body tries to contained the infection, to assist the activity, bone marrow supplies more leucocyte and as a consequence, we often find more immature band neutrophil in blood in patient having diarrhea and septic shock.[24] CRP is also an important inflammatory marker, higher level in septic shock compared to hypovolemic shock reflects the exaggerate effort of our body to fight the battle against pathogens in septic shock. Again, creatinine reflects renal response to fluid status and infection. In hypovolemic shock, there is increased probability of pre-renal kidney injury where as in diarrhea and septic shock, both fluid loss and infection poses insult to the kidney and kidney in response fails to work efficiently as a result, creatinine goes up and we observed higher creatinine both in hypovolemic shock and septic shock, however, higher value incase septic shock. From admission to 6 h follow up, mean/median POC lactate declined for the study participants. We also followed the gradient of fall in POC lactate from one time point to another time point and also between the groups. For, all the three gradients, values are lower for hypovolemic shock than for septic shock. It demonstrates mean/median POC lactate value decreases both in hypovolemic and septic shock, however, the decrease is lesser in septic shock group then in hypovolemic shock group. In hypovolemic shock, where fluid resuscitation restores cardiac circulation and thereby peripheral perfusion as well as renal perfusion, the decline in POC lactate is conceivable. Whereas in septic shock, the interplay is quite complex, initial fluid resuscitation though improves circulation, widespread endothelial injury, influences of circulating cytokines make the response transient with subsequent deterioration of the clinical condition unless other definitive goal directed therapy is not approached in a timely manner.

Limitation

The results of this study impart crucial evidence supporting the use of the POC lactate test to distinguish between septic shock and hypovolemic shock in patients with diarrhea. However, it is important to acknowledge and highlight certain limitations. Firstly, it should be noted that the study was conducted in a specialized hospital for diarrheal diseases, which means that the findings may not be applicable to a non-diarrheal situation. Furthermore, the absence of gold standard diagnostics, such as invasive hemodynamic monitoring through central venous pressure or point of care ultrasonography, hinders the ability to distinguish between septic shock and hypovolemic shock. Ultimately, the level of lactate can differ greatly among individuals owing to variations in lactate kinetics, which may affect the precision of point of care (POC) lactate measurements in both circumstances. Moreover, we could not analyze all the patients' data, especially the laboratory data mentioned in the footnote of Table 3, as those patients either expired or were referred to a different facility for specialized care. Finally, the post-hoc analysis for sample size might involve with circularity issues and conditional assumptions.

Despite these limitations, elevated POC lactate levels in severe dehydration in the absence of septic shock and sharp drop of lactate with adequate rehydration are the noblest findings of our observational study, which

warrant further scientific exploration prior a potential translation to clinical practice in achieving better patient care.

In conclusion, the results of our data suggest that the POC lactate test can detect septic shock differentiating from hypovolemic shock in diarrheal patients having variable levels of dehydration. However, no specific cut-off value is found to be highly sensitive as well as specific in differentiating septic shock from hypovolemic shock. Furthermore, the gradient of the POC lactate test may be a better predictor than a single measurement in differentiating septic shock from hypovolemic shock. The POC lactate test can also predict worse hospital outcomes, and that may be considered as a proof of concept for future intervention trial to have the mortality benefit.

Contributors

LS and MJC had contribution of the study concept and design. LS, MS, IP, MRN had full access of the data and responsible for data analysis with the guidance of TA and MJC. ASMSBS, IP and MMAH were responsible for data collection and project administration. LS, MS, IP, ASMSBS has drafted the manuscript with critical review from SNS, SN, MMAH and GMSM under the supervision of TA and MJC. Fund was arranged by TA.

Data sharing statement

The data used in this study can be obtained from the corresponding author upon reasonable request.

Declaration of interests

The authors have declared that no competing interests exist.

Acknowledgements

The development and conduction of the research was coordinated by the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b). We acknowledge Dr Daniel T Leung from Division of infectious Diseases, University of Utah School of Medicine, USA and Dr Adam Levine, The Warren Alpert Medical School of Brown University, USA for their insightful suggestions in developing the proposal. We acknowledge Dr Dennis Begos, the senior medical director of Medical and Scientific Affairs of Nova Biomedicals for providing POC lactate device for the research. Nova biomedical has no other contribution to the study design, data analysis or writing of the manuscript, neither they contributed in the funding of the research. We acknowledge the Global Affairs of Canada for their limited financial resources (GR-01686) for this study. We are also grateful to the Governments of Bangladesh and Canada for providing core and unrestricted support to icddr,b.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100500.

References

1 Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980â 2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459–1544.
2 Ferdous F, Ahmed S, Farzana F, et al. Aetiologies of diarrhoea in adults from urban and rural treatment facilities in Bangladesh. *Epidemiol Infect*. 2015;143(7):1377–1387.
3 Koh I, Liberatore A, Menchaca-Diaz J, et al. Bacterial translocation, microcirculation injury and sepsis. *Endocr Metab Immune Disord Drug Targets*. 2006;6(2):143–150.
4 Vaishnavi C. Translocation of gut flora and its role in sepsis. *Indian J Med Microbiol*. 2013;31(4):334–342.
5 Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):801–810.
6 Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43:304–377.
7 Shankar-Hari M, Phillips G, Levy M, et al. Assessment of definition and clinical criteria for septic shock. *JAMA*. 2016;315(8):762–774.
8 Andrews JR, Leung DT, Ahmed S, et al. Determinants of severe dehydration from diarrheal disease at hospital presentation: evidence from 22 years of admissions in Bangladesh. *PLoS Neglected Trop Dis*. 2017;11(4):e0005512.
9 Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200–211.
10 GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980±2015: a systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388(10053):1459–1544.
11 Sarmin M, Begum M, Islam F, et al. Factors associated with severe sepsis in diarrheal adults and their outcome at an urban hospital, Bangladesh: a retrospective analysis. *PLoS One*. 2021;16(9):e0257596.
12 Mohamed AKS, Mehta AA, James P. Predictors of mortality of severe sepsis among adult patients in the medical Intensive Care Unit. *Lung India*. 2017;34(4):330.
13 Liu Z, Meng Z, Li Y, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis. *Scand J Trauma Resuscitation Emerg Med*. 2019;27:1–10.
14 Hasan ST, Das S, Faruque A, Khan AI, Clemens JD, Ahmed T. Taking care of a diarrhea epidemic in an urban hospital in Bangladesh: appraisal of putative causes, presentation, management, and deaths averted. *PLoS Neglected Trop Dis*. 2021;15(11):e0009953.
15 Levine AC, Glavis-Bloom J, Modi P, et al. External validation of the DHAKA score and comparison with the current IMCI algorithm for the assessment of dehydration in children with diarrhoea: a prospective cohort study. *Lancet Global Health*. 2016;4(10):e744–e751.
16 Levine AC, Gainey M, Qu K, et al. A comparison of the NIRUDAK models and WHO algorithm for dehydration assessment in older children and adults with acute diarrhoea: a prospective, observational study. *Lancet Global Health*. 2023;11(11):e1725–e1733.
17 Tanner RK, Fuller KL, Ross ML. Evaluation of three portable blood lactate analysers: lactate Pro, lactate scout and lactate plus. *Eur J Appl Physiol*. 2010;109:551–559.
18 Baig MA, Shahzad H, Hussain E, Mian A. Validating a point of care lactate meter in adult patients with sepsis presenting to the emergency department of a tertiary care hospital of a low-to middle-income country. *World J Emerg Med*. 2017;8(3):184.
19 Kattan E, Ospina-Tascón GA, Teboul J-L, et al. Systematic assessment of fluid responsiveness during early septic shock resuscitation: secondary analysis of the ANDROMEDA-SHOCK trial. *Crit Care*. 2020;24:1–9.
20 Organization WH. *The treatment of diarrhoea: a manual for physicians and other senior health workers*. World Health Organization; 2005. Report No.: 9241593180.
21 Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749–1755.
22 Schmidt GA, Mandel J, Sexton DJ, Hockberger RS. *Evaluation and management of suspected sepsis and septic shock in adults*. Uptodate Online; 2018:1–29.
23 Minot A, Blalock A. Plasma loss in severe dehydration, shock and other conditions as affected by therapy. *Ann Surg*. 1940;112(4):557.
24 Stiel L, Meziani F, Helms J. Neutrophil activation during septic shock. *Shock*. 2018;49(4):371–384.