Associated Factors and Utility of Bed-side Assessment Tools to Avoid Antibiotic Overuse in an Urban ICU of a Developing Country

Farzana Afroz
   International Centre for Diarrhoeal Disease Research

Md. Tanveer Faruk
   International Centre for Diarrhoeal Disease Research

Mehnaz Kamal
   International Centre for Diarrhoeal Disease Research

Farhad Kabir
   International Centre for Diarrhoeal Disease Research

Monira Sarmin
   International Centre for Diarrhoeal Disease Research

Sharifuzzaman Sharifuzzaman
   International Centre for Diarrhoeal Disease Research

Mithun Chakraborty
   International Centre for Diarrhoeal Disease Research

Md. Rezaul Hossain
   International Centre for Diarrhoeal Disease Research

Shamima Sharmin Shikha
   International Centre for Diarrhoeal Disease Research

Visnu Pritom Chowdhury
   International Centre for Diarrhoeal Disease Research

Md. Zahidul Islam
   International Centre for Diarrhoeal Disease Research

Tahmeed Ahmed
   International Centre for Diarrhoeal Disease Research

Mohammad Jobayer Chisti (mailto:chisti@icddrb.org)
   International Centre for Diarrhoeal Disease Research

Research Article

Keywords: intensive care unit (ICU), Organ Dysfunction-2 (qPELOD-2), PICU, SIRS
Abstract

Antibiotic exposure in the intensive care unit (ICU) is very high, although 50% of all antibiotics may be unnecessary. We aimed to determine predicting factors, outcomes, and the utility of simple screening tools to avoid antibiotic overuse in the ICU. We analyzed 510 young children who did not receive antibiotics during ICU stay to those treated with antibiotics. The logistic regression analysis revealed that cases were more often older and independently associated with hypernatremia. Cases less often had severe underweight, altered mentation, age-specific fast breathing, lower chest wall in-drawing, adventitious sound on lung auscultation, abdominal distension, developmental delay, hyponatremia, hypocalcemia, and microscopic evidence of invasive diarrhea (for all, p<0.05). The case-fatality rate was significantly higher among the cases than the controls. For predicting 'no antibiotic approach,' the sensitivity of a negative quick Sequential Organ Failure Assessment (qSOFA) was similar to quick Pediatric Logistic Organ Dysfunction-2 (qPELOD-2) and higher than Systemic Inflammatory Response Syndrome (SIRS). In conclusion, 'No antibiotic approach' could be safely adopted in PICU using some simple clinical and laboratory characteristics, particularly in poor resource settings. A negative qSOFA or qPELOD-2 score calculated during PICU admission is superior to SIRS to avoid antibiotic overuse in under-five children.

Introduction

Appropriate use of antimicrobial agents is the cornerstone of effective antimicrobial stewardship programs, and has become a focus of patient safety, quality assurance, and health care outcomes. The Intensive Care Unit (ICU) deals with critically ill patients, and infections are among the most frequent causes of hospitalization among patients in the ICU. Thus antibiotic burden in ICU is very high; 66 to 77% of all ICU patients and 84-100% with an ICU stay of more than 48 hours are exposed to at least one class of broad-spectrum antibiotic\(^1,2\). As the definitive diagnosis of infection is often quite hard, Pediatric ICU (PICU) physicians are concerned about delayed treatment; consequently early initiation of broad-spectrum antibiotic is expected especially in the PICU settings\(^3,4\).

However, 50% of antibiotic prescriptions were inappropriate and could be avoided\(^5,6\). The situation is even worse in Low middle income countries (LMICs), where prescribing practices are poor, and antibiotic stewardship programs are frequently non-existent\(^7\). For instance, a study of antibiotic use in PICU showed that all children received antibiotics as prophylaxis (43%) or empirical (42%) therapy without having evidence of any infection, and 76% of children received two or more classes of antibiotics\(^8\). This inappropriate exposure upsurges the emergence of antimicrobial resistance leading to prolonged hospital stays and increases mortality as well as healthcare costs\(^9\text{-}11\).

Appropriate antibiotic prescribing is a complex decision-making process requiring the integration of epidemiological, clinical and microbiological knowledge and expertise in these fields. Improving diagnostic tools, and discriminate infections from non-infectious mimics, is the eventual solution to reducing unnecessary antibiotic initiation in the ICU. However, bacterial isolation by culture and
sensitivity, the gold standard test, is time-consuming and has low sensitivity for slow-growing and fastidious microorganisms\textsuperscript{12}. Although molecular diagnostic assays allow faster viral recognition, more rapid bacterial identification, and determination of antimicrobial susceptibilities\textsuperscript{13-15}, these are expensive and not always available in LMIC.

Several scoring systems have been developed to predict suspected infection or sepsis as a surveillance tool, and a positive score might be of value to identify infection promptly. Historically, the systemic inflammatory response syndrome (SIRS) criteria were considered to be fundamental to the diagnosis of inflammation and infection\textsuperscript{16}, although, it might not work in children with dehydration especially with diarrhea\textsuperscript{17}. Subsequently the quick Sequential Organ Failure Assessment (qSOFA) score (altered mentation, systematic hypotension and tachypnea)\textsuperscript{18,19}, and quick Pediatric Logistic Organ Dysfunction Score-2 (qPELOD-2) (altered mentation, systematic hypotension and tachycardia)\textsuperscript{20,21} have been recommended as a handy bedside tool to promptly recognize patients with infection who might be at risk of poorer outcomes, and could be predominantly useful in assessing critically sick patients. However, the utility of negative scores has not been validated to identify suspected non-bacterial infectious patients at ICU who would benefit from the watchful waiting approach.

Informative studies regarding whether clinicians could adopt a ‘watchful waiting’ and no antibiotic approach safely and confidently for a subset of PICU patients are still lacking. ICU physicians seldom consider a watchful waiting approach; in contrast, they prefer to overuse broad-spectrum antibiotics when faced with a non-reassuring characteristic\textsuperscript{22}. Thus, objective and evidence-based criteria are crucial to avoid unnecessary antibiotic exposure and, hence, tribulations. Therefore, we aim to identify the predictive factors and outcome of implementing a no antibiotic approach at PICU to prevent antibiotic overuse. We also evaluate the accuracy of negative SIRS, qSOFA, and qPELOD-2 scores in predicting no antibiotic or watchful waiting approach among young children presenting at the PICU with critical illness so that physicians can safely and confidently evade unnecessary antibiotic administration.

**Methods**

**Study site**

We have conducted this study at the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), located in Dhaka, Bangladesh's capital city. This hospital provides care for approximately 150,000 patients annually. Among them, sixty-two percent are aged below five years. Patients presenting with diarrhea with or without other comorbidities can seek health care at this hospital. The emergency department has a well-organized triage for sorting and prioritizing patients for care and initiating appropriate therapeutic measures. More than 90\% of patients are managed in the short-stay ward, where the median duration of stay is 18 hours. Only 1-2 \% of individuals needing immediate resuscitation at triage or patients with a critical illness or those with clinical deterioration in the short-stay ward or longer-stay ward are transferred to the ICU. The median duration of stay at the ICU is five days.
Study population and design

We conducted a retrospective observational study with an unmatched case-control design. Children aged 2-59 months admitted to the ICU of Dhaka Hospital with suspected critical illness between January 2017 and January 2020 were eligible for enrolment. We retrieved data through the hospital electronic database of the patient information system. Patients were considered to have critical illness if they met ICU transfer criteria following hospital guidelines (S1 File) and stayed in ICU for more than 24 hours. The cases were children who did not receive an antibiotic during their ICU stay and were discharged without antibiotic therapy. Children who received oral or parenteral antibiotics at triage or following ward transfer before admission in the ICU or during discharge were excluded.

In contrast, controls were children who received one or more intravenous antibiotic therapy during their stay at ICU. We assumed 85% exposure of acute watery diarrhea (AWD) in controls to compare the percentage of cases and controls, considering the high prevalence of AWD among children with high infection burden countries. To provide 80% power at a 5% level of significance (two-sided) and desired odds ratio (OR) of 2, we aimed to enroll 164 cases and 346 controls. Controls were selected using computer-generated random number sequences using SPSS version 20.0 for windows. The database identified 1821 controls, and 1:2 unmatched case-control ratios were used to increase the analyses' statistical power.

Measurement

We developed pretested case report form for the acquisition of relevant data. We reviewed all medical records, including the initial presentation to the triage, inpatient course, and outcome. Data on demographics (age, gender, breastfeeding, immunization as per EPI schedule), vital signs (temperature, heart rate, respiratory rate, mean arterial pressure, and SpO2), anthropometric measurements, clinical features (duration and consistency of diarrhea, duration of vomiting, dehydration status, documented seizure, altered mentation, developmental delay, congenital heart disease) and outcome were collected. We also examined laboratory results, including complete blood count, hypernatremia, hyponatremia, hyperkalemia, hypokalemia, metabolic acidosis, hypocalcemia, microscopic evidence of invasive diarrhea, UTI, and CNS infection, as well as bacterial pathogens from blood and stool culture those helped for no antibiotic approach.

Scoring systems

We calculated SIRS, qSOFA, and qPELOD-2 scores based on the first measured values after ICU entry. SIRS was defined as tachycardia, age-specific fast breathing, temperature abnormality (axillary temperature >38°C or <36°C), and white blood cell abnormality (>12000/mm3 or <4000/mm3 or bandemia >10%) in the absence of dehydration. SIRS score must include either temperature or white blood cell abnormality. qSOFA criteria were: hypotension, age-specific fast breathing, and altered mentation. qPELOD-2 criteria were: tachycardia, hypotension, and altered mentation. A threshold of fewer than two scores was applied to indicate a negative result for every score. We defined altered
mentation as having drowsiness, disorientation, confusion or coma. We defined age-specific fast breathing if the respiratory rate was >50 breaths/min for 2-11 months and >40 breaths/min for 12-59 months; tachycardia if the heart rate was ≥160 beats/min for 2-11 months, ≥140 beats/min for 12-59 months; and hypotension if mean arterial pressure <50 mm Hg.

**Management**

All children admitted to ICU were initially managed by trained ICU physicians following hospital guidelines. All children received standard treatment, including noninvasive or invasive oxygen therapy, intravenous fluid, suitable antibiotics (if necessary), antiseizure therapy for seizure, and other supportive management. We adopted a no antibiotic approach among the children who did not have severe acute malnutrition, sepsis 48, severe pneumonia (following WHO classification). During the initial clinical assessment, we evaluated history, physical examination and simultaneously rapid laboratory tests (complete blood count, stool for microscopic examination in diarrheal children, microscopic examination of urine and study of cerebrospinal fluid in children having a seizure) to identify any focus of bacterial infection. Attending physicians evaluated patients at least every 8 hours, and ICU consultants made clinical rounds at least twice a day. Antibiotics were added if the patient's condition deteriorated clinically, as discerned by the attending physician.

**Definition**

We defined severe stunting with a length or height for age z-score (LAZ/HAZ) < -3, severe underweight with weight for age z-score (WAZ) < -3 but ≥-4 ensuing WHO growth standards 49. We defined severe acute malnutrition (SAM) with a weight for length or height z score (WHZ) < -3 or weight for age z score (WAZ) < -4 of the median of the WHO anthropometry or presence of nutritional edema 50. We defined hypernatremia and hyponatremia if serum sodium concentration was >150.0 mmol/L and < 130.0 mmol/L; hyperkalemia and hypokalemia if serum potassium concentration was > 5.5 mmol/L and < 3.5 mmol/L; metabolic acidosis if serum TCO2 was < 17.0 mmol/L, hypocalcemia if serum calcium was < 2.12 mmol/L.

**Statistical analysis**

We analyzed data using the STATA for Windows (SAS Institute Inc.®, USA). We assessed the normality of distribution with the Shapiro-Wilk test. Continuous variables were expressed as mean ± SD or median (IQR), categorical variables as frequency and percentages. When comparing the no antibiotic and antibiotic groups, Student's t-test or Mann-Whitney's U test, as appropriate, was used to analyze the continuous variables. The Chi-square test or Fisher's exact test was used to compare differences in proportions. We applied multiple logistic regression analysis to identify the no antibiotic approach's determinants and the evolution of variables having a p < 0.05 at the bivariate analysis; OR were adjusted, and 95% confidence intervals were calculated.
The receiver operating characteristics (ROC) curve was created for each score. We determined each scoring system’s predictive accuracy using the AUROC (area under the receiver operating characteristics curve). We calculated sensitivity, specificity, positive and negative predictive values using contingency tables for every score. We compared the sensitivity and specificity of negative SIRS, qSOFA, and qPELOD-2 scores for no antibiotic approach using McNemar’s test and the AUROC using DeLong’s method \(^51\). A p-value of < 0.05 was considered statistically significant.

**Ethical Statement**

The data used in this study were retrieved from the electronic database of hospital patients’ records of the Dhaka Hospital of icddr, b. Data were recorded in an anonymized way before analysis and used to improve the quality of care of the hospital patients. However, the methods were carried out following the hospital guidelines and regulations. As we used de-identified data for this retrospective chart analysis, informed consent was not necessary. The Research Review and Ethical Review Committee of icddr, b waived the ethical approval for this de-identified data analysis and publication.

**Results**

In total, 2089 children aged 2 months to 59 months were admitted to the ICU of Dhaka Hospital between 2017 to 2020, and 268 (12.8%) children did not receive any antibiotic. We excluded 104 children because they were treated with antibiotics at emergency or after transferred to another ward. A final cohort of 510 children formed the analyzable data, 164 were cases, and 346 were controls. The mortality rate was significantly lower amongst the cases compared to controls (Table 1). The cases were more often older, presented with acute watery diarrhea, history of vomiting, seizure, and hypernatremia than the controls.

| Table 1. Sociodemographic and clinical characteristics of critically ill ICU children aged below five years without (cases) and with antibiotic therapy (controls) in Bangladesh. |
| Characteristics                              | Children without antibiotic (n=164) | Children with antibiotic (n=346) | OR   | 95% CI          | p-value |
|---------------------------------------------|------------------------------------|----------------------------------|------|-----------------|---------|
| Male                                        | 104 (63)                           | 211 (61)                         | 1.11 | (0.75 - 1.63)   | 0.598   |
| Age in months (median, IQR)                 | 10.1 (7.1, 14.0)                   | 8.1 (5.4, 12.3)                  | -    | -               | 0.002   |
| Breast feed                                 | 108 (65)                           | 218 (63)                         | 1.13 | (0.77, 1.67)    | 0.532   |
| Immunized as per EPI schedule               | 127 (77)                           | 261 (75)                         | 1.12 | (0.72, 1.74)    | 0.620   |
| Severe acute malnutrition                   | 0                                  | 119 (23)                         | -    | -               | -       |
| Severe stunting                             | 7 (4)                              | 86 (25)                          | 0.13 | (0.06, 0.30)    | <0.001  |
| Severe under weight                         | 11 (7) *                           | 132 (38)                         | 0.12 | (0.06, 0.22)    | <0.001  |
| Watery stool                                | 148 (90)                           | 287 (83)                         | 1.90 | (1.06, 3.42)    | 0.030   |
| Duration of diarrhoea                       | 152/164, 3.0 (2.0, 5.0)            | 313/346, 3.0 (2.0, 5.0)          | 0.19 | -               | -       |
| History of vomiting                         | 44 (27)                            | 66 (19)                          | 1.56 | (1.00, 2.41)    | 0.048   |
| Dehydration                                 | 39 (24)                            | 123 (36)                         | 0.56 | (0.37, 0.86)    | 0.008   |
| Fever                                       | 36 (22)                            | 97 (28)                          | 0.72 | (0.47, 1.12)    | 0.149   |
| Age specific fast breathing                 | 53/157 (34)                        | 176/340 (52)                     | 0.47 | (0.32, 0.70)    | <0.001  |
| Chest indrawing                             | 4 (2)                              | 89 (26)                          | 0.07 | (0.03, 0.20)    | <0.001  |
| Adventitious sound on lung auscultation     | 1 (0.6)                            | 119 (34)                         | 0.01 | (0.00, 0.08)    | <0.001  |
| Hypoxemia                                   | 2 (1) **                           | 59 (17)                          | 0.06 | (0.01, 0.25)    | <0.001  |
| Abdominal distension                        | 4 (2)                              | 42 (12)                          | 0.18 | (0.06, 0.51)    | <0.001  |
| Seizure                                     | 84 (51)                            | 106 (31)                         | 2.37 | (1.62, 3.48)    | <0.001  |
| Altered mentation                           | 41 (25)                            | 145 (42)                         | 0.46 | (0.30, 0.70)    | <0.001  |
| Condition                      | Cases       | Controls     | Odds Ratio (95% CI) | p-value |
|-------------------------------|-------------|--------------|---------------------|---------|
| Development delay             | 5 (3)       | 38 (11)      | 0.25 (0.09, 0.66)   | 0.003   |
| Congenital heart disease      | 3 (2)       | 23 (7)       | 0.26 (0.08, 0.88)   | 0.021   |
| Death                         | 0 (0)       | 8 (5.3)      | 0.044               |         |

* weight for age z-score <-3 but ≥-4. ** Hypoxemia due to congenital cyanotic heart disease.

In contrast, cases less often presented with SAM, severe underweight, severe stunting, dehydration, age-specific fast breathing, lower chest wall in-drawing, hypoxemia, adventitious sound on lung auscultation, abdominal distension, altered mentation, developmental delay, and congenital heart disease (Table 1). Similarly, Hyponatremia, hypokalemia, hyperkalemia, hypocalcemia, leukocytosis, and microscopic evidence of invasive diarrhea was less frequent among cases compared to their corresponding peers. Laboratory evidence of CNS infection and bacteremia were nil among cases. Similarly, bacterial pathogens isolated from stool culture were less frequent among cases compared to controls (Table 2).

**Table 2.** Laboratory characteristics of critically ill ICU children aged below five years without (cases) and with antibiotic therapy (controls) in Bangladesh.
| Characteristics                                      | Case (n=164) | Control (n=346) | OR   | 95% CI       | p-value |
|------------------------------------------------------|--------------|-----------------|------|--------------|---------|
| Hypernatremia                                        | 53 (32)      | 66 (19)         | 2.03 | (1.33, 3.09) | 0.001   |
| Hyponatremia                                         | 14 (9)       | 76 (22)         | 0.33 | (0.18, 0.61) | <0.001  |
| Hypokalaemia                                         | 46 (28)      | 128 (37)        | 0.66 | (0.44, 0.99) | 0.047   |
| Hyperkalaemia                                        | 7 (4)        | 44 (13)         | 0.31 | (0.13, 0.69) | 0.003   |
| Acidosis                                             | 92 (56)      | 210 (61)        | 0.83 | (0.57, 1.21) | 0.324   |
| Hypocalcaemia                                        | 36 (22)      | 115 (33)        | 0.56 | (0.37, 0.87) | 0.009   |
| Anaemia                                              | 87 (53)      | 184 (53)        | 0.99 | (0.68, 1.44) | 0.978   |
| Leukocytosis                                         | 75/140 (54)  | 203/318 (64)    | 0.65 | (0.44, 0.98) | 0.038   |
| Microscopic evidence of invasive diarrhoea           | 8 (5)        | 45 (13)         | 0.34 | (0.16, 0.75) | 0.005   |
| Laboratory evidence of CNS infection                 | 0            | 9 (3)           | -    | -            | 0.029   |
| Bacteremia                                           | 0            | 41 (12)         | -    | -            | <0.001  |
| Bacterial isolates from stool culture                | 3/17 (18)    | 41/177 (23)     | 0.71 | (0.19, 2.59) | 0.767   |

Using logistic regression models adjusted for potential confounders, the relative odds of no antibiotic approach increased in older children and the presence of hypernatremia. However, the relative odds decreased in the presence of severe underweight, altered mentation, age-specific fast breathing, lower chest wall indrawing, adventitious sound on lung auscultation, abdominal distension, developmental delay, hyponatremia, hypocalcemia, and microscopic evidence of invasive diarrhea (Table 3).

**Table 3. Logistic regression analysis revealing the independently associated factors for adopting no antibiotic approach in under-five ICU children in Bangladesh.**
| Characteristics                                | OR  | (95% CI)       | p-value |
|-----------------------------------------------|-----|----------------|---------|
| Male sex                                      | 1.44| (0.82, 2.54)   | 0.202   |
| Age in months                                 | 1.03| (1.01, 1.07)   | 0.024   |
| Hypernatremia                                 | 2.64| (1.31, 5.31)   | 0.006   |
| Hyponatremia                                  | 0.39| (0.17, 0.86)   | 0.021   |
| Hypocalcemia                                  | 0.46| (0.24, 0.89)   | 0.018   |
| Hyperkalemia                                  | 0.44| (0.15, 1.25)   | 0.122   |
| Acute watery diarrhea                         | 1.08| (0.45, 2.61)   | 0.856   |
| Dehydration                                   | 0.75| (0.39, 1.46)   | 0.401   |
| Severe stunting                               | 0.62| (0.19, 1.99)   | 0.423   |
| Severe underweight                            | 0.23| (0.08, 0.65)   | 0.005   |
| Altered mentation                             | 0.43| (0.23, 0.80)   | 0.008   |
| History of vomiting                           | 1.86| (0.96, 3.61)   | 0.066   |
| Age specific fast breathing                   | 0.88| (0.50, 1.55)   | 0.653   |
| Lower chest wall in-drawing                   | 0.16| (0.04, 0.61)   | 0.008   |
| Adventitious sound on lung auscultation       | 0.22| (0.00, 0.17)   | <0.001  |
| Abdominal distension                          | 0.18| (0.05, 0.60)   | 0.005   |
| Documented seizure                            | 1.50| (0.85, 2.65)   | 0.156   |
| Development delay                             | 0.32| (0.09, 1.10)   | 0.072   |
| Congenital heart disease                      | 0.39| (0.03, 4.65)   | 0.462   |
| Microscopic evidence of invasive diarrhea     | 0.19| (0.07, 0.48)   | <0.001  |
| Leukocytosis                                  | 0.94| (0.53, 1.67)   | 0.841   |

Of the included children, the frequency of SIRS, qSOFA, and qPELOD-2 negativity was 311/510 (61%), 452/510 (89%), and 475/510 (91%), respectively. Cases more often had SIRS, qSOFA, and qPELOD-negative children compared to controls (Fig 1). For predicting no antibiotic approach, a negative qSOFA and a negative qPELOD-2 both displayed a very high sensitivity of 95.9% (95% CI 91.8 to 98.3) and 95.9% (95% CI 91.8 to 98.3) respectively and low specificity of 17.1% (95% CI 13.2 to 21.4) and 13% (95% CI 9.6 to 17). Negative SIRS score had an intermediate sensitivity and specificity (Table 4).

**Table 4. Prognostic accuracy of scoring systems (95%CI) for predicting no antibiotic approach among under-five children in ICU, Bangladesh.**
Scores & Sensitivity % (95% CI) | Specificity % (95% CI) | NPV % (95% CI) | PPV % (95% CI)
--- | --- | --- | ---
Negative SIRS | 72.1 (64.8, 78.7) | 46.0 (40.6, 51.4) | 76.8 (70.5, 82.4) | 39.9 (34.4, 45.5)
Negative qSOFA | 95.9 (91.8, 98.3) | 17.1 (13.2, 21.4) | 89.4 (79.4, 95.6) | 36.5 (32.1, 41.1)
Negative qPELOD-2 | 95.9 (91.8, 98.3) | 13.0 (9.6, 17.0) | 86.5 (74.2, 94.4) | 35.4 (31.1, 39.9)

Area under the curve (95% CI) and comparison to AUROC

| Scores          | AUROC | 95% CI   | Comparison to AUROC     | P-value |
|-----------------|-------|----------|-------------------------|---------|
| Negative SIRS   | 0.59  | 0.59 (0.55, 0.63) | Negative SIRS vs. qPELOD-2 | 0.023   |
| Negative qSOFA  | 0.56  | 0.55 (0.54, 0.59) | Negative SIRS vs. qSOFA   | 0.262   |
| Negative qPELOD-2 | 0.54 | 0.53 (0.52, 0.57) | Negative qSOFA vs. qPELOD  | 0.071   |

All analyses used thresholds of SIRS<2, qSOFA<2, and qPELOD-2 score<2. AUROC, area under the receiver operating characteristics curve; ICU, intensive care unit; SIRS, Systemic Inflammatory Response Syndrome; qSOFA, quick Sequential Organ Failure Assessment; qPELOD-2, quick Pediatric Logistic Organ Dysfunction Score-2; NPV, Negative predictive value; PPV, Positive predictive value.

The AUROC of a negative SIRS, qSOFA, and the qPELOD-2 score is presented in figure 2 (Fig 2). The AUROC of a negative SIRS for predicting no antibiotic approach tends to be higher than a negative qPELOD-2 score (0.59 vs. 0.54; p-value=0.023). However, the AUROC between SIRS and qSOFA (0.59 vs 0.56; p-value=0.262) as well as between qSOFA and qPELOD-2 (0.56 vs 0.54; p-value=0.071) were comparable (Table 4).

**Discussion**

In this retrospective case-control study of 518 children aged 2 to 59 months admitted to an ICU of LMIC, we aimed to focus on the predictive factors and outcome of children who did not receive antibiotics. We also analyzed the accuracy of negative SIRS, qSOFA and qPELOD-2 scores for implementing no antibiotic approach in PICU. Some noteworthy observations were: first, no antibiotic approach more often implemented in older children and children with hypernatremia. Second, this approach less often implemented in severe underweight, altered mentation, age-specific fast breathing, chest in-drawing, adventitious sound on lung auscultation, abdominal distension, developmental delay, hyponatremia, hypocalcemia and microscopic evidence of invasive diarrhea. Third, we observed both negative qSOFA,
and qPELOD-2 scores showed higher sensitivity to identify children suitable for implementing no antibiotic approach, although the observations were compromised by lower specificity.

We found that antibiotic prescriptions were less in relatively older children. In this context, young infants are at increased risk for severe infection and often receive empirical antibiotic therapy. Rogawski et al. showed that antibiotic use was common in the first 6 months of life, even at the community level. The association of hypernatremia with no antibiotic approach in young diarrheal children is understandable. The most common cause of hypernatremia on admission is excess water loss due to acute watery diarrhea, and viral infections are responsible for most watery diarrhea cases. Empirical antibiotic treatment must be judiciously considered against inadvertent and potentially injurious consequences in such children.

Similarly, children showing microscopic evidence of invasive diarrhea and dysentery (visible blood in stool) should be treated with antibiotics as Shigella infection, associated with considerable mortality and morbidity, is suspected. However, eight children had microscopic evidence of invasive diarrhea, and three had bacterial isolates from their stool sample among children in no antibiotic group. These children had not been treated with antibiotics because their diarrhea resolved spontaneously before the availability of reports.

None of our cases had SAM. Several studies have revealed a high prevalence of infections among children hospitalized for SAM, and routine antibiotic therapy is recommended for such children. Children with severe underweight (WAZ <-3 but >-4) seem to be at considerably higher risk of infection compared to well-nourished children. A meta-analysis of more than five thousand children showed substantially higher mortality in underweight and wasted children than well-nourished children. We also observed less frequent implication of no antibiotic approach in children with severe underweight and stunting.

The association of less implication of no antibiotic approach in children with age-specific fast breathing, chest indrawing, adventitious sounds on lung auscultation is understandable. In LMIC, the diagnosis of pneumonia is based on cough and or breathing difficulty with clinical signs such as fast breathing and lower chest wall indrawing. The presence of hypoxemia is a sign of severe pneumonia. World Health Organization (WHO) recommended routine antibiotic therapy for childhood pneumonia to reduce mortality. In this study, the proportion of fast breathing and chest in-drawing among children who did not receive antibiotics was 15% and 2%, respectively, and none had a cough. Additionally, none of them had radiological evidence of pneumonia. These clinical signs without having a cough are known to be a nonspecific diagnostic tool for pneumonia, as most of our children had diarrhea, and our study children might demonstrate these signs mainly due to metabolic acidosis. We found two children in no antibiotic group had hypoxemia due to congenital cyanotic heart disease, so we did not include hypoxemia in the logistic regression model.
We found children who did not receive antibiotics less often had altered mentation, abdominal distension, hypocalcemia, and hyponatremia. Earlier studies have shown that altered mentation and abdominal distension in critically sick children might represent sepsis \(^{37}\) and should be treated with antibiotics. Studies have shown that total, and ionized calcium significantly reduced in sepsis. The mechanism of sepsis-induced hypocalcemia remains unknown; however, this appears to be associated with elevated levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-1, IL-6; hypoparathyroidism, vitamin D deficiency, or resistance \(^{38}\). Similarly, hyponatremia is commonly encountered in critically ill children with respiratory tract infections, sepsis and CNS infections. In a recent study, Park SW et al. reported that co-infection with multiple pathogens was more frequent in hyponatrexic children than in those without hyponatremia \(^{39}\).

Although clinicians often struggle to decide when to initiate antibiotics in critically ill children in ICU, still no study has examined the utility of negative SIRS, qSOFA, and qPELOD-2 scores as a bedside screening tool to overcome this challenging situation. We found negative qSOFA and qPELOD-2 with \(<2\) scores have high sensitivity of 96% for predicting no antibiotic approach, though no scoring system has high specificity. However, considering AUROC, negative SIRS \(<2\) scores is equivalent to qSOFA and more accurate than qPELOD-2. A previous study examining the performance of qSOFA demonstrated that the prevalence of PICU transfer and or mortality was 2% with qSOFA\(<2\) scores compared to 22.5% with qSOFA \(\geq 2\) in children presented to the emergency department \(^{40}\). The sepsis scoring systems have been developed to identify infection prompting immediate antibiotic therapy, though they lack sufficient sensitivity and specificity to capture sepsis. A prior study showed that the sensitivity and specificity of qSOFA were \(\geq 37\)% and 79%, respectively, and that or SIRS were \(\geq 80\)% and 21%, respectively, indicating neither scoring system truly identifies children requiring antibiotic therapy \(^{41}\).

**Limitation**

Our study result might not be generalizable because it was conducted in a single-center ICU of a diarrheal hospital. In developing countries, the PICU mortality ranges from 13-25\% \(^{42,43}\), though we observed relatively fewer death (5\%) in our cohort. We do not have a clear explanation for this; probably patients might not be as severe as in multi-disciplinary hospitals. However, in 2007 the mortality rate of our ICU was 11\% \(^{44}\). The introduction of bubble CPAP therapy as a standard of care for severe pneumonia with hypoxemia in under-five children since 2013 may be contributed for better outcomes \(^{45}\). Additionally, scrupulous adherence to management guidelines of SAM and other treatment protocols may impact this low mortality. The retrospective nature of the study is another important limitation.

**Conclusion**

This is the first study in the epoch of antibiotic resistance to determine predictive factors and outcomes associated with no antibiotic approach in ICU. We determined some simple independent predicting factors that might help ICU clinicians avoid overusing antibiotics in children, especially in resource-poor settings. Based on our findings, we may propose that ICU clinicians adopt no antibiotic or watchful
waiting approach in children with a qSOFA < 2 or qPELOD-2 score < 2. Our findings also suggest that the judicious implementation of the no antibiotic approach in PICU does not increase mortality risk than those treated with antibiotics. However, future prospective studies involving larger populations in different settings may consolidate our observation.

**Declarations**

**Acknowledgments**

We thankfully acknowledge the donors for their support and aptitude to icddr,b's research efforts. icddr,b is appreciative to the Governments of Bangladesh, Sweden, Canada, and the UK for providing fundamental support. We want to express our earnest thanks to all physicians, nurses, and other hospital members for their invaluable support in patient care.

**Author Contributions**

FA, MTF, MK, MS, SZ and MJC conceived and designed the study. FA, MTF, MK, MC, MRH, SSS, VPC, MFK and MZI were involved in collection and cleaning of data. FA and MJC analysed the data. MTF, MK, MFK, MS, SZ, MZI and MJC interpreted the data. FA, MJC provided the conceptual advice and MTF provided the technical support. FA, MTF, MK, MS, SZ, MFK, MC, MRH, SSS, VPC, MZI, TA and MJC contributed to the manuscript. All the authors approved the final version of the manuscript. MJC supervised and approved the final draft.

**Competing interests**

The authors declare no competing interests

**References**

1. De Bus, L. et al. A complete and multifaceted overview of antibiotic use and infection diagnosis in the intensive care unit: results from a prospective four-year registration. 22, 241 (2018).
2. Blinova, E. et al. Point prevalence survey of antimicrobial utilization in the cardiac and pediatric critical care unit. 14, e280-e288 (2013).
3. Levy, M. M., Evans, L. E. & Rhodes, A. J. I. c. m. The surviving sepsis campaign bundle: 2018 update. 44, 925-928 (2018).
4. Rhodes, A. et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. 43, 304-377 (2017).
5. Ceyhan, M. et al. Inappropriate antimicrobial use in Turkish pediatric hospitals: a multicenter point prevalence survey. 14, e55-e61 (2010).
6. Fontela, P. S. et al. Determinants of antibiotic tailoring in pediatric intensive care: A national survey. 18, e395-e405 (2017).
7. Thu, T. A. *et al.* Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *40*, 840-844 (2012).

8. Abbas, Q. *et al.* Evaluation of antibiotic use in pediatric intensive care unit of a developing country. *20*, 291 (2016).

9. El-Nawawy, A., Ashraf, G. A., Antonios, M. A., Meheissen, M. A. & El-Alfy, M. M. J. M. D. R. Incidence of multidrug-resistant organism among children admitted to pediatric intensive care unit in a developing country. *24*, 1198-1206 (2018).

10. Kociolek, L. *et al.* in *Open Forum Infectious Diseases*. (Oxford University Press).

11. Spellberg, B. *et al.* The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *46*, 155-164 (2008).

12. Dubourg, G. & Raoult, D. J. E. r. o. m. d. Emerging methodologies for pathogen identification in positive blood culture testing. *16*, 97-111 (2016).

13. Patel, R. in *Mayo Clinic Proceedings*. 1448-1459 (Elsevier).

14. Giebel, R. *et al.* in *Advances in applied microbiology* 71 149-184 (Elsevier, 2010).

15. Rogers, B. B. J. P. & Pathology, D. The evolution of the polymerase chain reaction to diagnose childhood infections. *18*, 495-503 (2015).

16. Goldstein, B., Giroir, B. & Randolph, A. J. P. c. c. m. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in Pediatrics. *6*, 2-8 (2005).

17. Chisti, M. J., Saha, S., Roy, C. N. & Salam, M. A. J. P. C. C. M. Predictors of bacteremia in infants with diarrhea and systemic inflammatory response syndrome attending an urban diarrheal treatment center in a developing country. *11*, 92-97 (2010).

18. Seymour, C. W. *et al.* Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *315*, 762-774 (2016).

19. Singer, M. *et al.* The third international consensus definitions for sepsis and septic shock (Sepsis-3). *315*, 801-810 (2016).

20. Leclerc, F., Duhamel, A., Deken, V., Grandbastien, B. & Leteurtre, S. J. P. C. C. M. Can the pediatric logistic organ dysfunction-2 score on day 1 be used in clinical criteria for sepsis in children? *18*, 758-763 (2017).

21. Leteurtre, S. *et al.* PELOD-2: an update of the PEdiatric logistic organ dysfunction score. *41*, 1761-1773 (2013).

22. Paño-Pardo, J. R. *et al.* Opportunities to improve antimicrobial use in paediatric intensive care units: a nationwide survey in Spain. *22*, 171-177 (2016).

23. Rogawski, E. T. *et al.* Use of antibiotics in children younger than two years in eight countries: a prospective cohort study. *95*, 49 (2017).

24. Bruce, H. (SAGE Publications Sage UK: London, England, 2012).

25. Kaiser, P., Borte, M., Zimmer, K.-P. & Huppertz, H.-I. J. E. j. o. p. Complications in hospitalized children with acute gastroenteritis caused by rotavirus: a retrospective analysis. *171*, 337-345 (2012).
26. Kotloff, K. L. et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *382*, 209-222 (2013).

27. Platts-Mills, J. A. et al. Pathogen-specific burdens of community diarrhoea in developing countries: a multisite birth cohort study (MAL-ED). *3*, e564-e575 (2015).

28. Williams, P. C., Berkley, J. A. J. P. & health, i. c. Guidelines for the treatment of dysentery (shigellosis): a systematic review of the evidence. *38*, S50-S65 (2018).

29. Afroze, F. et al. Risk factors and outcome of Shigella encephalopathy in Bangladeshi children. *11*, e0005561 (2017).

30. Organization, W. H. *Guideline: updates on the management of severe acute malnutrition in infants and children*. (World Health Organization, 2013).

31. Chisti, M. J. et al. Clinical risk factors of death from pneumonia in children with severe acute malnutrition in an urban critical care ward of Bangladesh. *8*, e73728 (2013).

32. Hooli, S. et al. Correction: predicting hospitalised paediatric pneumonia mortality risk: an external validation of RISC and mRISC, and local tool development (RISC-Malawi) from Malawi. *13*, e0193557 (2018).

33. McDonald, C. M. et al. The effect of multiple anthropometric deficits on child mortality: meta-analysis of individual data in 10 prospective studies from developing countries. *97*, 896-901 (2013).

34. Organization, W. H. Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. (2014).

35. Chisti, M. J. et al. Clinical predictors and outcome of metabolic acidosis in under-five children admitted to an urban hospital in Bangladesh with diarrhea and pneumonia. *7*, e39164 (2012).

36. Modi, P. et al. Oxygen saturation can predict pediatric pneumonia in a resource-limited setting. *45*, 752-760 (2013).

37. Chisti, M. J. et al. Severe sepsis in severely malnourished young Bangladeshi children with pneumonia: a retrospective case control study. *10*, e0139966 (2015).

38. Haghbin, S., Serati, Z., Sheibani, N., Haghbin, H. & Karamifar, H. J. T. I. J. o. P. Correlation of hypocalcemia with serum parathyroid hormone and calcitonin levels in pediatric intensive care unit. *82*, 217-220 (2015).

39. Park, S. W. et al. Hyponatremia in children with respiratory infections: a cross-sectional analysis of a cohort of 3938 patients. *8*, 1-9 (2018).

40. van Nassau, S. C. et al. Translating sepsis-3 criteria in children: prognostic accuracy of age-adjusted quick SOFA score in children visiting the emergency department with suspected bacterial infection. *6*, 266 (2018).

41. Goulden, R. et al. qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission in emergency admissions treated as sepsis. *35*, 345-349 (2018).
42. Naveed-ur-Rehman Siddiqui, Z. A., Jurair, H. & Haque, A. J. I. j. o. c. c. m. p.-r., official publication of Indian Society of Critical Care Medicine. Mortality patterns among critically ill children in a Pediatric Intensive Care Unit of a developing country. 19, 147 (2015).

43. Punchak, M. et al. Epidemiology of disease and mortality from a PICU in Mozambique. 19, e603 (2018).

44. Chisti, M. J., Pietroni, M. A., Smith, J. H., Bardhan, P. K. & Salam, M. A. J. A. p. Predictors of death in under-five children with diarrhoea admitted to a critical care ward in an urban hospital in Bangladesh. 100, e275-e279 (2011).

45. Chisti, M. J. et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. 386, 1057-1065 (2015).

46. Efunshile, A. M. et al. Apparent overuse of antibiotics in the management of watery diarrhoea in children in Abakaliki, Nigeria. 19, 1-7 (2019).

47. Schlapbach, L. J., Straney, L., Bellomo, R., MacLaren, G. & Pilcher, D. J. I. c. m. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. 44, 179-188 (2018).

48. Sarmin, M., Ahmed, T., Bardhan, P. K. & Chisti, M. J. J. A. p. Specialist hospital study shows that septic shock and drowsiness predict mortality in children under five with diarrhoea. 103, e306-e311 (2014).

49. Organization, W. H. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. (World Health Organization, 2006).

50. Chisti, M. J. et al. A prospective study of the prevalence of tuberculosis and bacteraemia in Bangladeshi children with severe malnutrition and pneumonia including an evaluation of Xpert MTB/RIF assay. 9, e93776 (2014).

51. DeLong, E. & DeLong, D. (Pearson DL. Comparing the Areas Under Two or More).

**Figures**
Figure 1

Distribution of included children without and with antibiotic therapy according to the percentage of negative (<2 scores) SIRS, qSOFA, and qPELOD-2 criteria met.
Figure 2

ROC curves of negative (<2 scores) SIRS, qSOFA and qPELOD-2 criteria for predicting no antibiotic therapy at ICU. ICU, intensive care unit; SIRS, Systemic Inflammatory Response Syndrome; qSOFA, quick Sequential Organ Failure Assessment; qPELOD-2, quick Pediatric Logistic Organ Dysfunction Score-2; ROC, receiver operating characteristics curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S1File.docx