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Development and validation of the "Pediatric Risk of Nosocomial Sepsis (PRiNS)" score for health care–associated infections in a medical pediatric intensive care unit of a developing economy—a prospective observational cohort study☆

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ABSTRACT

Purpose: Given the high burden of health care–associated infections (HAIs) in resource-limited settings, there is a tendency toward overdiagnosis/treatment. This study was designed to create an easy-to-use, dynamic, bedside risk stratification model for classifying children based on their risk of developing HAIs during their pediatric intensive care unit (PICU) stay, to aid judicious resource utilization.

Materials and methods: A prospective, observational cohort study was conducted in the 12-bed PICU of a large Indian tertiary care hospital between January and October 2011. A total of 412 consecutive admissions, aged 1 month to 12 years with PICU stay greater than 48 hours were enrolled. Independent predictors for HAIs identified using multivariate regression analysis were combined to create a novel scoring system. Performance and calibration of score were assessed using receiver operating characteristic curves and Hosmer-Lemeshow statistic, respectively. Internal validation was done.

Results: Age (<5 years), Pediatric Risk of Mortality III (24 hours) score, presence of indwelling catheters, need for intubation, albumin infusion, immunomodulator, and prior antibiotic use (≥4) were independent predictors of HAIs. This model, with area under the ROC curve of 0.87, at a cutoff of 15, had a negative predictive value of 89.9% with overall accuracy of 79.3%. It reduced classification errors from 29.8% to 20.7%. All 7 predictors retained their statistical significance after bootstrapping, confirming the internal validity of the score.

Conclusions: The "Pediatric Risk of Nosocomial Sepsis" score can reliably classify children into high- and low-risk groups, based on their risk of developing HAIs in the PICU of a resource-limited setting. In view of its high sensitivity and specificity, diagnostic and therapeutic interventions may be directed away from the low-risk group, ensuring effective utilization of limited resources.

1. Introduction

Health care–associated infections (HAIs) from pediatric intensive care units (PICUs) are reported to the tune of 6% to 13.7% and are a major cause of morbidity and mortality worldwide [1-4]. Timely detection and administration of antibiotics are crucial in improving outcomes in children with life-threatening HAIs. A few studies from the developed world have attempted to use biomarkers such as C-reactive protein, procalcitonin, and others to identify infections and decide regarding initiation of antibiotic therapy in intensive care units (ICUs) [5-7]. In developing economies, decision to treat with antibiotics is largely based on clinical judgment due to limited availability of the aforementioned point-of-care testing or other sepsis biomarkers. This leads to overtreatment and contributes to a huge financial burden in resource-limited settings [8]. In addition, inappropriate empirical use of high-end antibiotics increases the risk of emergence of multidrug-resistant superbugs.

There is an urgent need, therefore, to identify the subset of children that is at a low risk for acquiring HAIs, so as to reduce or eliminate overtreatment with antibiotics and also to ensure effective utilization of limited resources. Identifying these children can be challenging. Although adult and neonatal prediction models have been devised, there is a paucity of pediatric models applicable beyond the neonatal age group

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[9-13]. Moreover, those existing have limitations in that they are either single-point assessments or emphasize more on admission variables [14,15]. Hence, the current study was designed to evolve an easy-to-use, dynamic, bedside, risk stratification score for HAIs in the medical PICU of a developing economy.

2. Materials and methods

This was a single-center, prospective observational cohort study, in which we first developed the score and then validated it within the same cohort using 2 techniques: a temporal, nonrandom split and bootstrapping technique. This study was carried out in the 12-bed medical PICU of a large tertiary care teaching and referral hospital in Northern India after seeking ethical approval from the institute committee. Our PICU predominantly handles medical conditions with a high caseload of infectious diseases. We do not routinely cater to polytrauma, burns, and primary surgical diagnoses. The PICU is equipped with all advanced monitoring facilities including invasive hemodynamic, respiratory, and neurologic monitoring. The nurse-patient ratio is 1:1 for ventilated and 1:2 for nonventilated children.

All children admitted between January and October 2011, having PICU stay of at least 48 hours, were eligible for enrollment. Our PICU admits children in the age group of 1 month to 12 years, and hence, only children in this age bracket were enrolled in this study. Children with hematological malignancies were excluded from the study, as they have a distinct risk factor and microbiological profile.

Only children of the parents who provided informed consent were enrolled. The enrolled children were monitored at least twice a day by the pediatric critical care fellows and once daily by the PICU consultant for clinical signs of infection. Health care–associated infections were diagnosed based on the Center for Disease Control and Prevention (CDC) surveillance definitions [16-18] (Appendix 1) in the children after 48 hours of PICU admission and within 72 hours of transfer from PICU. For the derivation of the score, only those with positive microbiological results (culture-positive cases) from relevant body fluids were included.

2.1. Other definitions

For the purpose of this score derivation, the following terms were defined as described herewith:

- "Indwelling catheters"—Central venous line, arterial lines, urinary catheters, intercostal drainage tubes, etc. (excluding peripheral intravenous catheters and endotracheal tubes) existing at the point of assessment or removed within the previous 48 hours [19,20]. Endotracheal tube was not included in the "indwelling catheters" and was considered a separate risk factor, in view of its strong association with ventilator-associated pneumonia.
- "Immunomodulator usage"—Use of intravenous immunoglobulin or steroids at anytime until the point of assessment.
- "Prior antibiotic use"—Number of antibiotics received until the point of assessment [17].

2.2. Data collection

The data collection was done on a predesigned proforma by a team, not directly involved in the management of the child, to avoid bias. Data collection was continuous (daily) for all children. Demographic details, Pediatric Risk of Mortality III (PRISM III-24) score, severity of malnutrition (World Health Organization [WHO] Z scores [21]), presence of sepsis at admission, comorbidities (if any), indication for PICU transfer, duration of outside hospital as well as emergency ward stay, and others were noted for every patient. Details related to indwelling catheters (device utilization and duration of each catheter); intubation (duration of intubation and need for reintubation); ventilation (length of ventilation, mean airway pressures, fraction of inspired oxygen requirement, settings, etc); medications (sedoanalgesia, neuromuscular blockers, antibacterials, antivirals, antifungals, etc); vasoactive infusions (inotrope score [22]); nutrition (enteral and parenteral, adequacy of calorie-protein intake, etc); temperature variability (fever spikes or hypothermia episodes); laboratory markers of infection (total leucocyte counts, absolute neutrophil counts, C-reactive protein, etc); other laboratory, radiologic and microbiological (all body fluid cultures) tests; transport [19] (intrahospital and interhospital); and blood product use were also documented. All details relevant to HAIs (focus, severity, outcome, antimicrobial therapy, etc) were documented.

Patients were followed up prospectively throughout duration of PICU stay and 72 hours thereafter. The standard HAI prevention policies (ventilator-associated pneumonia prevention bundle, central line–associated bloodstream infection prevention bundle, hand hygiene practices, appropriate isolation practices, etc) have been in place in our PICU since 2009 and remained unchanged during the study period. The compliance to these bundles was monitored as part of the routine weekly nursing audits.

2.3. Data management and statistical analysis

The sample size for the development of this model was calculated based on need for "10-15 children with event (HAI) per risk factor" plus a 20% anticipated dropout [23-25]. A total of at least 100 episodes of culture-positive HAIs are required for derivation of a reliable score. Based on the incidence rate in our PICU, the period for data collection was calculated to be 10 months.

Each episode of HAI was considered as a distinct event for the purpose of derivation of the score. Admission variables (demographic details, PRISM III-24 score, etc) were used as such for both the groups. For other parameters (indwelling catheters, intubation, ventilation, antibiotics, vasoactive infusions, etc), data available to the bedside clinician at the point of suspicion of HAI (ie, data of the previous 24-48 hours) were used for the "HAI" group; whereas for the "no-HAI" group, maximum exposure time (until transfer out of PICU or death) was taken into consideration. For example, "number of antibiotics" until the point of suspicion of HAI was used for the HAI group, whereas "total number of antibiotics received until transfer out of PICU or death" was used for the "no-HAI group." For the various markers of infection for the no-HAI group, peak values of various parameters were used for comparison.

A univariate logistic regression first identified the predictors. Each predictor was transformed into categorical variable using either cutoffs available in literature or a robust locally weighted least squares regression between occurrence of HAI and the continuous variables using the locally weighted scatterplot smoothing function [26,27]. Locally weighted scatterplot smoothing was used to examine change in log odds or probability of outcome along a gradient of the continuous predictor, based on which a cutoff point was identified. All variables that emerged as predictors on univariate analysis were screened for clinical relevance by experts in pediatric critical care (MJ and SS) based on existing literature and biological plausibility. Similarly, the categorization/dichotomization created based on statistical techniques was also verified for clinical relevance.

χ^2 Test and Fisher exact test were used for categorical variables. Continuous variables were analyzed with t test or Kruskal-Wallis test. When 2 or more parameters on univariate analysis had high correlation (correlation coefficient >0.7), the more clinically appropriate variable was chosen for inclusion in model derivation.

The model was derived using multivariate logistic regression with stepwise backward elimination likelihood ratio method with adjustment for clustering. Calibration of the model was assessed using Hosmer-Lemeshow test and the discrimination, using receiver operating characteristic (ROC) curves [24,25]. The final "Pediatric Risk of Nosocomial Sepsis (PRiNS) score" was created based on the regression coefficients in the logistic regression model. Internal validation was