Epidemiology of Bleeding in Critically Ill Children

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Objective To determine the epidemiology of bleeding in critically ill children.

Study design We conducted a cohort study of children <18 years old admitted to the pediatric intensive care unit for >24 hours and without clinically relevant bleed (CRB) on admission. CRB was defined as resulting in severe physiologic derangements, occurring at a critical site or requiring major therapeutic interventions. Using a novel bleeding assessment tool that we developed, characteristics of the CRB were abstracted from the medical records independently and in duplicate. From the cohort, we matched each child with CRB to 4 children without CRB based on onset of CRB. Risk factors and complications of CRB were identified from this matched group of children.

Results We analyzed 405 children with a median age of 35 months (IQR 7-130 months). A total of 37 (9.1%) children developed CRB. The median number of days with CRB was 1 day (IQR 1-2 days). Invasive ventilation (OR 61.35; 95% CI 6.27-600.24), stress ulcer prophylaxis (OR 2.70; 95% CI 1.08-6.74), surgical admission (OR 0.29; 95% CI 0.10-0.84), and aspirin (OR 0.04; 95% CI 0.002-0.58) were associated with CRB. CRB was associated with longer time to discharge from the unit (hazard ratio 0.20; 95% CI 0.13-0.33) and the hospital (hazard ratio 0.49; 95% CI 0.33-0.73). Children with CRB were on vasopressor longer and transfused more red blood cells after the CRB than those without CRB.

Conclusions Our findings suggest that bleeding complicates critical illness in children. *(J Pediatr 2017;184:114-9).*

Bleeding complicates critical illness in adults.[1] Approximately 6%-20% of adults admitted to the intensive care unit (ICU) develop major bleed, which is a clinically relevant bleed (CRB) resulting in severe physiologic derangements, occurring at a critical site or requiring major therapeutic intervention.[1,2] An additional 8%-70% of them develop a minor bleed, which is an overt bleed that is less severe than a major bleed. Decrease in platelet count, prolongation of activated partial thromboplastin time, heparin at therapeutic doses, antiplatelet agents, renal replacement therapy, and recent surgery are associated with a major bleed. Compared with those with no bleeds, critically ill adults with major bleeds are transfused with larger amounts of blood products, stay longer in the ICU, and have higher risks of mortality.

Bleeding may also complicate critical illness in children. However, the epidemiology (ie, incidence, risk factors and complications) of bleeding in these children is unclear. Studies have focused on selected children admitted to the ICU with illnesses or therapies that increase bleeding risk. These studies report that 3%-52% of the children bleed while admitted.[3-9] The uncertainty in the estimates is partly due to inconsistencies in the definitions used for bleeding. Recently, the International Society on Thrombosis and Hemostasis (ISTH) defined categories of bleeding to standardize outcomes in clinical trials of anticoagulation.[10] Aside from major and minor bleeds, as previously defined, the category of clinically relevant nonmajor bleeds was added for bleeding that does not fulfill the criteria for a major bleed but required transfusion of blood products, or medical or surgical intervention other than in an operating suite to restore hemostasis. In this study, we developed a novel bleeding assessment tool based on the definitions recommended by ISTH. Using this tool, we aimed to determine the epidemiology of bleeding in an unselected cohort of critically ill children.

Methods

The study was composed of 2 phases. In phase 1, we developed the bleeding assessment tool, and then pilot tested it in a cross-sectional study. In phase 2, we performed a cohort study to determine the incidence of bleeding. Risk factors and complications associated with bleeding were identified in a nested case-control study. The study was approved by the Human Investigation Committee at Yale University, which waived the need for signed consent.

CRB	Clinically relevant bleed
HR	Hazard ratio
ICU	Intensive care unit
ISTH	International Society on Thrombosis and Hemostasis

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Phase 1

Development of the Bleeding Assessment Tool. One of the investigators created the electronic tool that contained the definitions recommended by ISTH for major, clinically relevant nonmajor, and minor bleed (**Appendix**; available at www.jpeds.com). Items used to categorize a bleed were described in sufficient detail in the tool to maximize consistency in its use. The tool also contained the site and timing of the bleed. It was revised after discussion among all investigators.

Pilot Testing of the Bleeding Assessment Tool. Using an electronic patient database, children admitted to the pediatric ICU at Yale-New Haven Children's Hospital from January 1, 2013, to December 31, 2013, with a diagnosis of a bleed were randomly selected. The investigators blindly and independently reviewed the medical records of 10 children per cycle. The first bleed for every child was categorized using the bleeding assessment tool. In between cycles, the entire investigative team discussed the cases and resolved discrepancies. The process was repeated until the chance-corrected inter-rater agreement (κ) was ≥0.80.

Phase 2

Subjects. A cohort of children less than 18 years old who were admitted to the pediatric ICU at Yale-New Haven Children's Hospital from January 1, 2014, to December 31, 2014, were randomly selected using the electronic patient database. Excluded were those who stayed in the ICU for less than 24 hours because they were mostly admitted for observation. For those with multiple admissions, 1 admission was randomly selected. Children who had a CRB, whether major or nonmajor, upon admission were excluded after review of medical records. We analyzed major and nonmajor CRBs together because both categories, by definition, are clinically significant and have the potential to impact the child's health and outcome.

Each child with a CRB (case) was randomly matched to 4 children without a CRB (control). The day of stay in the ICU when the CRB first occurred in cases were matched to a similar time point in controls (match day). Matching based on time leads to complete adjustment for the effect of duration of stay in the ICU and its determinants.[11]

Procedures. The medical records of each eligible child were blindly and independently reviewed by 2 randomly assigned investigators. The bleeding assessment tool was completed by each investigator for each bleed. A third randomly assigned investigator adjudicated discrepancies in the categorization of the bleed.

The investigator primarily assigned to each child also collected from the medical records data on demographics; medications, interventions, and worst laboratory tests at any time while admitted to the ICU; and, outcomes. Collection of daily data was censored at 14 days, which represented the 95th percentile of the duration of stay in our ICU. Predicted risk of mortality was calculated based on the Pediatric Index of Mortality 2.[12] Anticoagulants included unfractionated heparin except at doses to maintain patency of a vascular catheter, low molecular weight heparin, and warfarin, whereas antifibrinolytics included tranexamic and aminocaproic acid. Stress ulcer prophylaxis included proton pump and histamine H_2 receptor inhibitors. Vasopressor use was defined as dopamine ≥5 mcg/kg/min, or any dose of dobutamine, epinephrine, norepinephrine, phenylephrine, milrinone, and vasopressin. Respiratory support was categorized as invasive ventilation via endotracheal tube or tracheostomy, noninvasive ventilation (ie, continuous or bilevel positive airway pressure, or high flow nasal cannula greater than 5 L/min for children less than 10 years old and greater than 8 L/min for children at least 10 years old) or none, which included any support that did not qualify for invasive or noninvasive ventilation. Extracorporeal support included extracorporeal membrane oxygenation, renal replacement therapy, and erythro- or leukapheresis. Cryoprecipitate was included in plasma transfusion.

Statistical Analyses

In phase 1, crude inter-rater agreement and κ were calculated. Bleeds were dichotomously categorized based on the presence of a CRB in calculating κ. Furthermore, agreement was defined as a majority of investigators assigning the same category. In a sensitivity analysis, κ was calculated based on the presence of any bleed.

In phase 2, the incidence of bleeding was expressed as proportion of children and days in the ICU with bleed. Conditional logistic regression with stepwise backward elimination at an exit threshold of $P > .05$ was used to identify factors associated with a CRB. Data on potential risk factors were limited to a specific number of days prior to match day. When applicable, the time period was based on pharmacokinetics (ie, 7 days for aspirin, 5 days for warfarin, and 1 day for unfractionated heparin, low molecular weight heparin, tranexamic acid, aminocaproic acid, vasopressor, and heparin for extracorporeal support). For others, it was arbitrarily set at 2 days based on consensus among investigators. Multiple imputations using multivariate normal distribution was used for missing laboratory data. Times to outcome, adjusted for age, and predicted risk of mortality, were compared between cases and controls using Cox regression with shared frailty model to account for the matching. Number of days on vasopressors and volume of blood products transfused from match day were compared between cases and controls using linear mixed effects model with matching as random effect. Use of vasopressors or blood product transfusion prior to match day, and duration of stay in the ICU from match day were entered as fixed effects. Data was expressed as median (IQR), mean difference (95% CI), count (percentage), OR (95% CI), and hazard ratio (HR; 95% CI). In the absence of reliable estimates of the proportion of critically ill children with bleed, 405 children were analyzed assuming a true proportion of 0.50. This provided the largest sample size for a 95% CI of ±0.05.

All analyses were performed in Stata v 14 (StataCorp, College Station, Texas). A 2-sided P value of <.05 was considered statistically significant.