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Epidemiology of Bleeding in Critically Ill Children With an Underlying Oncologic Diagnosis

OBJECTIVES: Critically ill children with malignancy have significant risk of bleeding but the exact epidemiology is unknown. We sought to describe severe bleeding events and associated risk factors in critically ill pediatric patients with an underlying oncologic diagnosis using the newly developed Bleeding Assessment Scale in Critically Ill Children definition.

DESIGN: Retrospective cohort study.

SETTING: PICU in comprehensive cancer center,

PATIENTS: Children ages 28 days to 18 years with an underlying oncologic diagnosis admitted to the PICU during 2018.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Two-hundred sixty-seven admissions met inclusion criteria. Sixty-four percent (171/267) were male, with a median (interquartile range) age of 6.3 years (3.1–12.1 yr). Nine percent (23/267) had at least one severe bleeding event during their PICU admission. There were no significant differences between those with severe bleeding and those without, with respect to gender ($p = 0.07$), age ($p = 0.66$), weight ($p = 0.76$), or transplant status ($p = 0.18$). There was a difference in the frequency of severe bleeding based on underlying oncologic diagnosis ($p = 0.009$). For patients with severe bleeding, the median (interquartile range) platelet count and international normalized ratio on the day of bleeding were $102 \times 10^9/L$ ($40\text{--}181 \times 10^9/L$) and 1.36 (1.26–1.51), respectively. Eighty-seven percent patients (20/23) with severe bleeding received at least one blood component in response to bleeding. Two patients received antifibrinolytics. Patients with severe bleeding had significantly fewer PICU-free days ($p = 0.001$), fewer ventilator-free days ($p < 0.001$), and higher 28-day mortality ($p = 0.003$).

CONCLUSIONS: Severe bleeding occurred in nearly one-tenth of critically ill children with an underlying oncologic diagnosis without severe thrombocytopenia or coagulopathy. The vast majority received blood component therapy, but few received hemostatic medication. Studies are needed to guide the treatment of severe bleeding in this vulnerable patient population.

KEY WORDS: bleeding; blood transfusion; cancer; children; coagulopathy; critical illness; thrombocytopenia

Although bleeding can be a common complication of critical illness in children, there are currently limited epidemiologic data on the frequency of its occurrence. Two retrospective studies have reported that approximately 10% of critically ill children have at least one clinically relevant bleeding event during their admission to the ICU (1, 2). One limitation in reporting the epidemiology of bleeding is that until recently, there was no validated tool used to quantify bleeding in pediatric critical illness. With the advent of the Bleeding Assessment Scale in Critically Ill Children (BASIC), a validated, objective tool used to define mild, moderate, and severe bleeding

Juliana Romano, MD¹

Mario Martinez, MD¹

Julie Levasseur, MD, MPH¹

James S. Killinger, MD^{2,3}

Oliver Karam, MD, PhD⁴

Marianne E. Nellis, MD, MS^{2,3}

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in the PICU, epidemiologic studies to examine the frequency of bleeding are now possible (3).

Several studies have demonstrated the adverse consequences of bleeding events in critically ill adults. Bleeding has been shown to be independently associated with increased mortality in adults with acute coronary syndrome (4) and after bone marrow transplant (5). Major bleeding has also been shown to be associated with longer ICU length of stay in critically ill adults (6). In the pediatric population, bleeding has been shown to be associated with increased duration of vasoactive support, increased RBC transfusions, and longer PICU and hospital stays (2).

In addition to the factors that put all critically ill children at risk of bleeding such as disseminated intravascular coagulation, liver dysfunction affecting coagulation, or renal failure and uremia that can affect platelet function, critically ill children with an underlying oncologic diagnosis have additional risk factors that may increase their likelihood of bleeding. Children with an oncologic diagnosis frequently have bone marrow suppression, either from their chemotherapeutic regimen or from marrow infiltration by the underlying disease, leading to hypoproliferative thrombocytopenia (7, 8). They undergo invasive procedures, ranging from placement of a central venous catheter to the surgical resections of large intra-abdominal or brain tumors. Despite the many risk factors for bleeding, there are scarce data to describe the epidemiology of bleeding in this vulnerable patient population.

In this study, we sought to describe the epidemiology of severe bleeding events in critically ill children with an underlying oncologic diagnosis, as well as associated risk factors and clinical outcomes.

METHODS

Population and Setting

We conducted a retrospective cohort study of children admitted to the PICU at Memorial Sloan Kettering Cancer Center (MSKCC) during 2018. The study was reviewed and approved by the Institutional Review Board of MSKCC (Protocol 19-058). MSKCC is a Comprehensive Cancer Center with a five-bedded PICU that receives both medical and surgical admissions for patients followed at MSKCC for their underlying illness. Patients receive blood transfusions as per the discretion of the critical care provider based on the clinical scenario.

There were no transfusion protocols for the critically ill child, either for prophylaxis or to treat bleeding.

Children were included if they were 28 days to 18 years old. All patients had either a diagnosis of cancer or had undergone stem cell transplantation for an oncologic or nononcologic indication. Patients were excluded if they were preterm infants less than 44 weeks corrected gestational age at time of enrollment or term infants less than 28 days old, if there was a documented limitation of care at enrollment, such as a standing do-not-resuscitate order. Additionally, patients were excluded if they were transferred to another PICU during their admission.

Severe bleeding was defined by BASIC as outlined in **Table 1** (3). Data were collected from the MSKCC electronic medical record. Demographic information, underlying oncologic diagnosis, admission diagnoses, organ dysfunction score at admission (9), and clinical outcomes including 28-day PICU-free days, 28-day ventilator-free days, and mortality were collected on all admissions. Of note, the criteria for severe bleeding and admission diagnoses were not mutually exclusive; patients could have more than one in each category. In the group of patients who had a severe bleeding event during the admission, information on the bleeding event, including blood transfusions received, use of hemostatic medications (e.g., tranexamic acid [TXA]), discontinuation of anticoagulation, surgical interventions, laboratory values, and hemodynamic values, were collected.

Statistical Analysis

Demographic and clinical characteristics were described as *n* (%) or median and interquartile range (IQR), as appropriate. Admissions with at least one severe bleeding event were compared with admissions without severe bleeding events by chi-square/Fisher exact tests or Wilcoxon rank-sum tests. A sensitivity analysis of unique patients was completed to evaluate the association when excluding repeat admissions of the patients who were admitted more than once during the course of the year. Two-sided *p* values below 0.05 were considered significant. All analyses were conducted using SPSS Version 25 (IBM Corp, Armonk, NY).

RESULTS

Data were collected on 267 admissions, representing 192 unique patients, with 75 patients admitted more

TABLE 1.**Definition of Severe Bleeding According to Bleeding Assessment Scale in Critically Ill Children Definition**

“Any” of the following criteria define “severe bleeding”:

- Bleeding that leads to at least one organ dysfunction, using Pediatric Logistic Organ Dysfunction-2 score criteria of organ dysfunction, within 24 hr of the previous assessment (if there is no previous assessment, the baseline results are presumed to be normal). The organ dysfunction should be associated with the bleeding, in absence of other causes
- Bleeding that leads to hemodynamic instability, defined as an increase in heart rate by > 20% from baseline or a decrease in blood pressure by > 20% from baseline. The hemodynamic instability should be associated with the bleeding, in absence of other causes
- Bleeding leading to a drop in hemoglobin > 20% within 24 hr. The drop in hemoglobin should be associated with the bleeding, in absence of other causes
- Quantifiable bleeding ≥ 5 mL/kg/hr for ≥ 1 hr (e.g., chest tube, drain)
- Intraspinal bleeding leading to loss of neurologic function below the lesion, nontraumatic intra-articular bleeding leading to decreased range of movement, or intraocular bleeding leading to impaired vision

than once. Sixty-four percent of patient admissions (171/267) were male, with a median (IQR) age of 6.3 years (3.1–12.1 yr). The most common underlying oncologic diagnosis was neuroblastoma, representing 38% (102/267) of the admissions. This was followed by sarcomas at 24% (63/267) and primary CNS cancers at 12% (33/267). Twelve percent (33/267) of patient admissions in the total cohort had undergone prior bone marrow transplant. Over half of the admissions (61%, 164/267) were postoperative, with the most common surgery being thoracoabdominal resections (33%, 54/167). The median (IQR) Pediatric Logistic Organ Dysfunction-2 score on day of admission was 2 (2–4).

At least one severe bleeding event occurred in 9% (23/267) of patient admissions while in the PICU. Of the admissions with severe bleeding, the most commonly met criteria was “bleeding leading to a drop in hemoglobin (Hb) > 20% within 24 hours” in 70% (16/23) of the cases. Less commonly, children with severe bleeding had bleeding leading to at least one organ dysfunction (26%, 6/23), bleeding leading to hemodynamic instability (26%, 6/23), quantifiable bleeding greater than 5 mL/kg/hr (4%, 1/23), or intraspinal, intra-articular, or intraocular bleeding (4%, 1/23).

Table 2 describes the differences in patient characteristics between the patient admissions with severe bleeding and those without. There were no significant differences between those with severe bleeding and those without with respect to gender ($p = 0.07$), age ($p = 0.66$), weight ($p = 0.76$), hematopoietic stem cell transplant status ($p = 0.18$), or prior chimeric antigen

receptor T-cell therapy ($p = 0.38$). There was a difference seen in the frequency of severe bleeding based on underlying oncologic diagnosis ($p = 0.009$). In addition, hemorrhagic shock was the only admitting diagnosis that demonstrated a significant difference between the two groups ($p = 0.007$).

Median (IQR) laboratory values on the day of severe bleeding are displayed in **Table 3**. Of note, the patients with severe bleeding in general only had mild thrombocytopenia, mild coagulopathy, and mild hypofibrinogenemia. The median (IQR) platelet count, international normalized ratio (INR), and fibrinogen on the day of bleeding was $102 \times 10^9/L$ (40–181 $\times 10^9/L$), 1.36 (1.26–1.51), and 155 mg/dL (152–237 mg/dL), respectively. **Supplemental Table 1** (<http://links.lww.com/CCX/A841>) describes the mean and ranges of these values. No patients underwent viscoelastic testing.

Eighty-seven percent patients (20/23) with severe bleeding received at least one blood component in response to the bleeding. RBC transfusion was the most common (83%, 19/23), followed by plasma (35%, 8/23), platelets (30%, 7/23), and cryoprecipitate (4%, 1/23). Four patients (17%) had a surgical procedure in response to the severe bleeding. One thoracostomy tube was placed, one ventriculoperitoneal shunt was placed, one patient underwent spinal cord decompression, and one patient underwent embolization of an arterial aneurysm by interventional radiology. Two patients (9%) received TXA in response to the severe bleeding; none received desmopressin, aminocaproic acid, or activated factor VII. No patients were on anticoagulation at the time of the bleeding event.

TABLE 2.
Comparison of Characteristics of Each Admission Between Those With Severe Bleeding and Those Without Severe Bleeding

Admission Characteristics	Severe Bleeding Event During Admission?		<i>p</i>
	No (<i>n</i> = 244)	Yes (<i>n</i> = 23)	
Gender, <i>n</i> (%)			0.070
Male	152 (62)	19 (83)	
Female	92 (38)	4 (17)	
Age, yr, median (IQR)	6.3 (3.1–11.9)	7.7 (2.1–15.1)	0.663
Weight, kg, median (IQR)	21 (14–40)	18 (8–57)	0.758
Oncologic diagnosis, <i>n</i> (%)			0.009
Leukemia	23 (9)	1 (4)	
Lymphoma	1 (0.5)	2 (9)	
Neuroblastoma	97 (40)	5 (22)	
Primary CNS	31 (13)	2 (14)	
Sarcoma	55 (23)	8 (35)	
Wilms tumor	6 (3)	0 (0)	
Other oncologic	19 (8)	3 (13)	
Nononcologic	12 (5)	2 (9)	
Prior hematopoietic stem cell transplant, <i>n</i> (%)	28 (12)	5 (22)	0.179
Prior chimeric antigen receptor T-cell therapy, <i>n</i> (%)	8 (3)	0 (0)	0.378
Postoperative admission, <i>n</i> (%)	153 (63)	11 (48)	0.161
Thoracoabdominal resection	50 (21)	4 (17)	0.752
Thoracotomy	22 (9)	3 (13)	0.376
Orthopedic procedure	11 (5)	3 (13)	0.055
Neurosurgical procedure	28 (12)	1 (4)	0.691
Other	44 (18)	1 (4)	0.292
Admitting diagnosis, <i>n</i> (%) ^a			
Respiratory insufficiency/failure	22 (9)	4 (17)	0.195
Cardiac insufficiency/failure	2 (1)	0 (0)	0.663
Hemorrhagic shock	0 (0)	2 (9)	0.007
Tumor lysis syndrome	1 (0.5)	0 (0)	0.758
Hypertensive urgency/emergency	5 (2)	1 (4)	0.477
Veno-occlusive disease	2 (1)	0 (0)	0.663
Increased intracranial pressure	10 (4)	2 (9)	0.309
Encephalitis	1 (0.5)	0 (0)	0.758
Seizure	8 (3)	1 (4)	0.786
Septic shock	9 (4)	2 (9)	0.248

IQR = interquartile range.

^aAdmitting diagnoses are not mutually exclusive.

Clinical outcomes for the children with severe bleeding versus those without are presented in **Table 4**. Seven patients died (7/192, 4%) during their PICU admission.

Patients with severe bleeding had significantly fewer PICU-free days ($p = 0.001$), fewer ventilator-free days ($p < 0.001$), and higher 28-day mortality ($p = 0.003$).

TABLE 3.
Laboratory Assays on Day of Severe Bleeding (*n* = 23)

Laboratory Assays	Median (IQR)
Lowest platelet count ($\times 10^9/L$)	102 (40–181)
Highest prothrombin time (s)	16.7 (15.5–18.1)
Highest partial thromboplastin time (s)	31.5 (29.5–38.6)
Highest international normalized ratio	1.36 (1.26–1.51)
Lowest fibrinogen (mg/dL)	155 (151–237)
Lowest hemoglobin (g/dL)	6.5 (5.9–7.9)

IQR = interquartile range.

The sensitivity analysis of the 192 unique patients examining all reported variables showed no differences in the results described above.

DISCUSSION

Critically ill children with underlying oncologic diagnoses are at significant risk of bleeding. We report that nearly 9% had at least one episode of severe bleeding. The severe bleeding events occurred despite relatively normal standard hemostatic assays. Most patients received the transfusion of at least one blood component in response to the severe bleeding, but few received hemostatic medications. Severe bleeding was associated with worse clinical outcomes including time on the ventilator, time in the PICU, and mortality.

Despite being evaluated in a specific subpopulation of critically ill children, our reported rate of bleeding appears similar to those reported previously in general PICUs (1, 2). However, these studies reported

TABLE 4.
Clinical Outcomes in Children With Severe Bleeding Versus Those Without Severe Bleeding

Clinical Outcomes, Median (IQR)	Severe Bleeding		<i>p</i>
	No (<i>n</i> = 244)	Yes (<i>n</i> = 23)	
PICU-free days	25 (23–26)	23 (0–25)	0.001
Mechanical ventilation-free days	28 (28–28)	28 (15–28)	< 0.001

IQR = interquartile range.

All clinical outcomes were censored at 28 d.

the rates of “clinically relevant bleeding” that might include both moderate and severe bleeding according to the BASIC definition (3). Therefore, the rate of severe bleeding we observed may, in fact, be higher than previously reported.

What factors put these children at risk of severe bleeding compared with children without an oncologic diagnosis? Our cohort had relatively normal standard hemostatic measures. Previous studies of children with oncologic diagnoses have shown that even mild thrombocytopenia may increase the risk of bleeding compared with adults with similar platelet counts (10), and therefore, it may be reasonable to consider mild thrombocytopenia as a risk factor for severe bleeding in our cohort. However, studies in adults have shown that patients only require approximately $7 \times 10^9/L$ to maintain effective hemostasis (11). Similarly, prothrombin time and/or activated partial thromboplastin time are traditional measures of the time it takes for blood to form a clot after *in vitro* incubation with thromboplastin and therefore can be used as an estimation of adequate coagulation. However, conventional coagulation testing has demonstrated poor predictive value for bleeding in adults undergoing invasive procedures (12) and in subpopulations of critically ill children including neonates (13) and children supported by extracorporeal membrane oxygenation (14). It is possible that viscoelastic testing, which measures the whole blood’s ability to clot, may be of value to predict bleeding in critically ill children with an oncologic diagnosis. While its value in decreasing the number of transfusions has been reported in children undergoing cardiopulmonary bypass surgery (15, 16) and patients with chronic liver disease (17), it has not been adequately assessed in our patient population.

We report that one-third of critically ill children with an oncologic diagnosis and severe bleeding received either plasma and/or platelet transfusions in response to the bleeding event. A recent point prevalence study of platelet transfusion practice in over 200 children with cancer admitted to the PICU reported that one-third of transfusions were administered for bleeding indications but could not establish any association of platelet transfusions with improvement in bleeding outcomes (18). Similarly, studies on the use of plasma transfusions in critically ill children only demonstrated significant changes (i.e., decrease in INR) following plasma (transfusion) when the pretransfusion INR was greater

than 2.5 (19). Given the significant increase in morbidity and mortality associated with both platelet and plasma transfusions in critically ill children (20, 21), the efficacy of these products in bleeding critically ill children with oncologic diagnoses deserves further study.

Few children in our cohort received hemostatic medications. Antifibrinolytic medications, such as TXA or aminocaproic acid, may be of benefit in critically ill children with an oncologic diagnosis, especially in postsurgical patients. The use of these medications has been shown to reduce bleeding and transfusion requirements in children undergoing cranial vault repairs (22, 23), as well as repair of scoliosis (24). However, the efficacy of TXA in cancer patients has been limited to adult case reports (25). Although there is theoretical concern for the risk of clotting with antifibrinolytics, small studies in adults with cancer have not demonstrated an increased risk (26). The use of antifibrinolytics to treat bleeding in children with oncologic diagnoses should be explored.

Last, we found that severe bleeding was associated with poorer clinical outcomes in our cohort. Our work provides preliminary evidence that the BASIC definition may be useful to more adequately describe bleeding in this subgroup of critically ill children compared with previously used bleeding scales.

There are several strengths to this study. The study was performed in a specialized cancer hospital, and therefore, we were able to assess a relatively large population of critically ill children with an underlying oncologic diagnosis in a relatively short period of time. We present not only patient risk factors for severe bleeding but also descriptive reports of the interventions used in response to bleeding.

Some limitations exist. The study is observational and, as such, can only demonstrate associations and not causations. The data come from a single center with a high volume of surgical cases and may not be generalizable to other similar patient populations. Because the BASIC definition relies on a provider being able to attribute clinical or laboratory changes to bleeding alone, and not other pathophysiologic reasons for these changes, some subjectivity exists. Given the retrospective nature of the study, the incidence of severe bleeding noted may not be a true reflection of that found in a prospective study of a similar patient population. For example, it is much easier to attribute a

drop in hemoglobin to bleeding alone if one can follow the patient in real time. It is possible that the changes in physiologic and laboratory measures were overattributed to bleeding, and therefore, our report of the incidence of bleeding is overestimated. We found an association between the patient's underlying oncologic diagnosis and the presence of severe bleeding. This may be in part due to the higher intensity of certain chemotherapeutic regimens, such as those used to treat sarcomas. However, these data were not collected.

CONCLUSIONS

In our cohort of critically ill children with an underlying oncologic diagnosis, severe bleeding occurred in nearly one-tenth of admissions, despite absence of severe thrombocytopenia or coagulopathy. The majority of patients received blood component therapy but not hemostatic medications. Studies are needed to guide the treatment of severe bleeding in this vulnerable patient population.

1 Department of Pediatrics, New York-Presbyterian/Weill Cornell Medicine, New York, NY.

2 Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY.

3 Division of Pediatric Critical Care, Department of Pediatrics, Weill Cornell Medicine, New York, NY.

4 Division of Pediatric Critical Care Medicine, Children's Hospital of Richmond at VCU, Richmond, VA.

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For information regarding this article, E-mail: man9026@med.cornell.edu

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