CLINICAL LABORATORY VARIABLES ASSOCIATED WITH CLINICALLY SIGNIFICANT BLEEDING IN PEDIATRIC INTENSIVE CARE UNIT PATIENTS

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Clinical and Laboratory Variables Associated with Clinically Significant Bleeding in Pediatric Intensive Care Unit Patients

by

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Abstract

Existing research into clinically significant bleeding in Pediatric Intensive Care Unit (PICU) patients is limited to specific bleeding sites and specific patient groups. Existing literature does not accurately describe the epidemiology of clinically significant bleeding in the PICU and may not correctly identify potential risk markers. Using a broadly inclusive definition of clinically significant bleeding, we conducted a retrospective cohort study of PICU patients and identified clinical risk markers including mechanical ventilation, antibiotic and antacid medications, performance of multiple procedures, and cardiac surgery. A threshold for platelet count associated with clinically significant bleeding in PICU patients was also identified, but other common laboratory tests of hemostasis had no association. We designed a prospective observational cohort study to further examine the association of laboratory tests with clinically significant bleeding. Platelet count was again associated with clinically significant bleeding, but the International Normalized Ratio (INR) and the activated Partial Thromboplastin Time (PTT) were not. This association was present even after adjustment for potentially confounding clinical variables. These results suggest that thrombocytopenia is an important and potentially modifiable risk factor for clinical significant bleeding in PICU patients.

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List of Abbreviations and Symbols

CHEO	Children's Hospital of Eastern Ontario
CI	Confidence Interval
EBV	Estimated Blood Volume
HIT	Heparin Induced Thrombocytopenia
HR	Hazard Ratio
INR	International Normalized Ratio
LMWH	Low Molecular Weight Heparin
OR	Odds Ratio
PICU	Pediatric Intensive Care Unit
PRISM	Pediatric RISk of Mortality score
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time
UFH	Unfractionated Heparin

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Chapter 1: Introduction and Overview

1.1 Introduction

Bleeding is a potential danger for critically ill patients, such as those in the pediatric intensive care unit (PICU), who have a variety of underlying medical and surgical conditions. Uncontrolled hemorrhage can have significant consequences for patients, such as organ dysfunction, hypotension, and even death. Bleeding, when it occurs, can also have significant implications for patient management, including the use of blood products and medications, surgical management of bleeding, and delays in required investigations and treatments. However, despite the potential importance of bleeding in the PICU, the epidemiology of this problem has not been adequately described in the literature. Tools for the identification of PICU patients at risk of significant bleeding are not available. Although there are a variety of medical therapies available for the prevention and treatment of bleeding (platelet concentrates, vitamin K, fresh frozen plasma, cryoprecipitate, tranexamic acid, aminocaproic acid, and recombinant activated human factor VII), optimal evidence-based strategies for the use of these therapies are not known.

1.2 Definition of Clinically Significant Bleeding

Not all bleeding presents a danger to the patient or requires intervention. Minor bleeding from venipuncture sites, small abrasions and lacerations in trauma patients, and trivial bleeding into surgical dressings are all examples of bleeding that is not clinically important. Studies that examine bleeding in PICU

patients, then, must be careful to define bleeding that is considered clinically significant.

Significant or excessive bleeding in PICU patients or post-surgical pediatric patients has been defined using a variety of criteria. In pediatric cardiac surgery patients, the volume of post-operative chest tube drainage, which can be directly measured, has been used to classify bleeding, with significant blood loss being defined as post-operative chest tube drainage greater than 20% of estimated blood volume (EBV) during the first 2 hours in the PICU, greater than 20% of EBV during the interval between hours 2 and 6 in the PICU, or greater than 30% of EBV during the interval between hours 6 and 12 in the PICU(1,2).

Bleeding that results in changes in clinical management has also been classified as significant, including: bleeding requiring medical or surgical intervention(3); and severe post-operative bleeding requiring re-operation or moderate bleeding causing loss of 10 – 20% of estimated blood volume or requiring readmission to hospital for intravenous fluids and observation(4).

Some studies have combined some of the above categories of information with results of laboratory tests and clinical observations of patients to define significant bleeding. These *composite* definitions of significant bleeding include: overt gastrointestinal bleeding plus either a decrease in systolic blood pressure of at least 20 mmHg from baseline, an increase in heart rate of at least 20 beats per minute from baseline, or a decrease in hemoglobin concentration of at least 20 g / L from baseline(5); overt gastrointestinal blood loss that, within 48 hours, results in a decrease in hemoglobin concentration of 20 g / L, hypotension, red blood cell

transfusion, multiple organ system failure, surgical management of the bleeding, or death(6); and macroscopic gastrointestinal hemorrhage with hematologic or hemodynamic repercussions such as a decrease in hematocrit of more than 15 percentage points, hypotension, or a need for volume resuscitation, transfusion, or pressors(7).

What is clear from this disparate literature is that there is no consistent definition of clinically significant bleeding in the literature. A variety of types of information have been used to define clinically significant bleeding, including direct measurement of blood loss, the occurrence of specific interventions after bleeding, changes in laboratory data, and changes in patient condition. Moreover, to date, only bleeding from specific sites, such as chest tubes or the gastrointestinal tract, was considered and composite definitions that have been used have only involved a few component criteria.

A broadly-inclusive definition of clinically significant bleeding, which attempts to capture the wide range of possible physiologic effects of bleeding on patients, sites of bleeding, and clinical management decisions in response to bleeding, has not been used in any study of PICU patients. (Such a broadly-inclusive composite definition of significant bleeding has successfully been applied prospectively to adult intensive care unit patients(8).) As a result, the studies that currently exist do not describe the epidemiology of all significant bleeding in the PICU, and therefore may underestimate the frequency of clinically significant bleeding in PICU patients.

1.3 Incidence of Clinically Significant Bleeding in PICU Patients

The studies describing the incidence of clinically significant bleeding in a general PICU population have only considered gastrointestinal bleeding, and have provided estimates of this incidence from 1.6% (95% CI 0.8% - 2.4%) (6) to 5.3% (no confidence interval reported) (5).

Currently available estimates of the incidence of significant hemorrhage in PICU patients show considerable variation. Although this may represent different incidences in different study populations, or different incidences that result from definitions of significant bleeding that vary between studies, it may indicate a poor understanding of the basic epidemiology of clinically significant bleeding in the PICU. As previously discussed, the existing literature likely underestimates the frequency of phenomenon.

1.4 Timing of Clinically Significant Bleeding After Admission to the PICU

Few studies have systematically addressed the timing of significant bleeding after admission to the PICU and these studies have been limited to surgical patients. In one series of patients undergoing surgery for idiopathic adolescent scoliosis, hemorrhagic complications requiring intervention did not occur more than 7 days after surgery(3). Using a definition of excessive bleeding based on chest tube output, 94% of cardiac surgery patients who had excessive bleeding did so within 6 hours of admission to the PICU(1).

Existing literature only provides information on the likely timing of significant bleeding for patients admitted to the PICU in small subgroups of post-operative patients. This makes it difficult for the clinician to determine the time

frame after admission during which it is most important to monitor patients for bleeding. This situation also makes study of clinically significant bleeding in the PICU more difficult, as the time frame during which bleeding events are most likely to be observed is unknown.

1.5 Common Laboratory Tests as Predictors of Clinically Significant Bleeding in PICU Patients

Platelet count, prothrombin time (PT) or international normalized ratio (INR), and activated partial thromboplastin time (PTT) are commonly used laboratory tests of hemostasis that have been used to attempt to predict bleeding in some settings. However, systematic evaluations of the utility of these tests for predicting bleeding risk in general populations of PICU patients are limited.

In a prospective study of central venous catheter placement in PICU patients, patients were described as having a "bleeding diathesis" based on cut-off values that appear to have been chosen arbitrarily: patients who had platelets < 50, PT > 20 s, or PTT > 40 s were said to have a "severe diathesis"; and patients who had platelets between 50 and 100, PT between 17 s and 20 s, or PTT between 35 s and 40 s were said to have a "mild diathesis". (According to these definitions, 21% of patients had a bleeding diathesis.) There were 369 catheter placements and no episodes of clinically significant bleeding occurred in any patient, with or without a bleeding diathesis, indicating that this definition of bleeding diathesis based on commonly-used laboratory tests had poor predictive ability for significant bleeding(9).

In another study of PICU patients, thrombocytopenia (platelet count < 100)

was a risk factor for significant gastrointestinal hemorrhage using a univariate analysis, but not using a multivariate analysis(5). "Coagulopathy", defined as a platelet count less than 100 or PT, PTT, or thrombin time greater than 20% above a control value, was associated with an increased risk of clinically significant upper GI bleeding in PICU patients(6). In these studies, the cut-off values used to identify patients who may have impaired hemostasis do not appear to have been evidence-based.

The small number of studies that examine the ability of platelet count, PT/INR, and PTT to predict clinically significant bleeding in PICU patients provide conflicting results, and do not convincingly demonstrate that these tests have a role in identifying patients with increased bleeding risk. This could be due, in part, to the fact that not all forms of bleeding were considered by these studies. If bleeding other than gastrointestinal bleeding had been considered, more bleeding events would likely have been observed, and it might have been possible to demonstrate associations between bleeding and laboratory tests that met criteria for statistical significance.

Alternatively, it may be that these laboratory tests do not predict bleeding risk. In pediatric patients undergoing tonsillectomy/adenoidectomy, the inability of PT/INR and PTT to identify patients with increased risk of post-operative bleeding has been established, as abnormalities of these tests have been shown to have poor sensitivity and positive predictive value for bleeding(4,10,11). Although this patient group differs from PICU patients in many important respects, it is still a population subject to a risk of clinically significant

hemorrhage. These studies therefore cast considerable doubt on the use of PT/INR and PTT as measures of global hemostatic function or as indicators of bleeding risk in pediatric patients. However, the limitations of existing studies of PICU patients and the potential importance of being able to reliably identify patients with increased bleeding risk indicate that this area is in need of further study.

1.6 Clinical Factors as Predictors of Clinically Significant Bleeding in PICU Patients

Some studies have looked at the bleeding risk associated with patient characteristics or with aspects of a patient's clinical condition or management in the PICU. A series of pediatric cardiac surgery patients found that post-operative chest tube output was associated more strongly with age than with any laboratory test(2). Another study of pediatric cardiac surgery patients found that patient weight of less than 8 kg was associated with increased post-operative chest tube output(12).

A study of PICU patients found that mechanical ventilation was a risk factor for significant gastrointestinal bleeding and that prophylactic ranitidine (an antacid medication) did not decrease the frequency of significant bleeding. The authors speculate that the high frequency of dengue hemorrhagic fever in their patients may have reduced the effectiveness of antacid prophylaxis, meaning that these results may not be generalizable to other settings(5).

Another study found that univariate predictors of clinically significant gastrointestinal bleeding in PICU patients included intubation, mechanical

ventilation, acute respiratory distress syndrome, gastric tube placement, enteral feeding, organ system failure, and high PRISM score. (The Pediatric Risk of Mortality score is a validated tool for predicting mortality in PICU patients.) Other predictive variables were antacid prophylaxis, which was associated with increased risk, and surgical procedures, which were associated with decreased risk. (These two findings, in particular, are counter-intuitive.) Multivariate analysis found that respiratory failure, coagulopathy, and PRISM equal to or greater than 10 were the only independent risk factors, and that risk of significant bleeding was 18.8% in those patients with all three risk factors(6).

The literature shows that clinical factors, such as patient age and weight, intubation and ventilation, use of prophylactic antacid medication, surgical procedures, and family history of bleeding, may have some predictive value. Furthermore, in one study the value of clinical data was greatest when combined with laboratory evidence of decreased hemostatic potential. These findings suggest that clinical data should be included in any attempt to identify factors associated with increased risk of clinically significant bleeding.

1.7 Summary and Research Plan

The existing literature describing clinically significant bleeding in the PICU is limited in important respects. The epidemiology of clinically significant bleeding and its sequelae are poorly described. Although there are common laboratory tests that evaluate some parts of the hemostatic system, they have not been convincingly demonstrated to predict bleeding risk for PICU patients. Improved understanding of the predictive ability of these tests, or the lack of this ability,

would be desirable.

We hypothesized, then, that applying a broadly-inclusive definition of clinically significant bleeding to PICU patients would demonstrate that clinically significant bleeding is more common in this population than is currently thought. We further hypothesized that the number of bleeding events identified with this definition would be sufficient to identify and evaluate possible risk markers – including clinical and laboratory data – for clinically significant bleeding in PICU patients.

In order to test these hypotheses, we conducted a pilot retrospective cohort study that was followed by a prospective observational cohort study of PICU patients at a single institution.

Co-Authorship Statement

Paul C Moorehead was the principal investigator, designed the studies, collected data, analyzed data, wrote the manuscripts, and approved the final version of the manuscripts.

Janelle Cyr collected data, wrote parts of the Introduction and Methods in Chapter 2, and approved the final version of that manuscript.

Nicholas J Barrowman participated in statistical aspects of study design, analyzed data, and wrote sections of the Methods describing techniques of statistical analysis in Chapters 2, and approved the final version of that manuscript.

Robert Klaassen is one of the senior investigators and approved the final version of the manuscripts.

Kusum Menon is one of the senior investigators and approved the final version of the manuscripts.

Chapter 2: A Retrospective Cohort Study of Risk Markers for Clinically Significant Bleeding in the Pediatric Intensive Care Unit

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2.1 Introduction

Significant or excessive bleeding is of particular concern for critically ill patients, and can have serious consequences such as organ dysfunction and death. Despite the potential morbidity of significant bleeding for patients in the pediatric intensive care unit (PICU), existing research on such bleeding in PICU patients is limited. Studies are restricted to particular patient groups (e.g. cardiac surgery patients(1,2,12)) or to particular sites of bleeding (e.g. chest tube(1,2,12) or gastrointestinal tract(5–7)). Consequently, existing studies of the epidemiology and potential risk factors for clinically significant bleeding in PICU patients may not accurately describe all bleeding in an unrestricted population of PICU patients.

We hypothesized that applying a broadly-inclusive composite definition of clinically significant bleeding to an unrestricted population of PICU patients would demonstrate a higher incidence of clinically significant bleeding than had

previously been observed. We conducted a retrospective cohort study to examine the incidence and timing of clinically significant bleeding and to identify possible risk factors.

2.2 Methodology

This retrospective cohort study took place at the Children's Hospital of Eastern Ontario (CHEO), a university-associated pediatric tertiary care centre servicing a population of approximately 1.5 million. The CHEO PICU is a 10 bed unit that admits approximately 600 patients per year, including post-operative cardiovascular surgery patients. The average length of stay in this unit is 3.9 days; 57.4% of admitted patients are ventilated; the average Pediatric Risk of Mortality (PRISM) score for admitted patients is 5, and the mortality rate is 3.1% (CHEO PICU database). This study was approved by the Research Ethics Board at CHEO.

Standardized case report forms (Appendix 1) with instructions (Appendix 2) were developed, and a research assistant was trained in their use. Throughout the data collection, there were frequent meetings between the principal investigator and research assistant to discuss data abstraction and coding.

Electronic medical records were used to identify all patients admitted to the PICU between January 1st 2009 and June 30th 2009, inclusive. Patients 18 years of age and older were outside the pediatric age group, and were excluded. It is possible that newborns would need to be studied separately because of their age and size. Furthermore, there are significant differences in coagulation factor

levels between older children and newborns, and these differences are present *at least* until 30 days of age(13)(14). For these reasons, patients less than 60 days of age or weighing less than 5 kg were excluded. Other exclusion criteria were admission to the PICU because of bleeding, presence of a previously diagnosed inherited bleeding disorder, and prior eligible admission to the PICU during the study period. Patients who did not meet any exclusion criteria were eligible for further data collection.

Both paper and electronic records of eligible patients were examined. Baseline data from the time period beginning 24 hours prior to admission and ending 6 hours after admission (an arbitrarily-chosen time point, by which time it was assumed that the initial workup of the patient on admission to the PICU would have been completed) were collected. These data included: demographic information, including gender, age, weight, and reason for PICU admission; clinical information, including vital signs, oral intake, need for respiratory support, use of medications (antibiotics, steroids, antacids, anti-hemostatics, pro-hemostatics), use of blood products, and procedures performed; and laboratory information, including complete blood count, transaminases, renal function tests, blood gases, and coagulation tests (PTT and INR). If a blood test was performed multiple times for one patient, only the result from the time closest to the time of admission was collected. Results and events that occurred after an episode of clinically significant bleeding (defined below) were not included in the data collection or subsequent analysis.

Patients were assumed to have received standard care and monitoring

during their PICU admissions. This would have included routine clinical monitoring for bleeding from the mouth, nose, and rectum, as well as bleeding from surgical and other wounds, gastric tubes, endotracheal tubes, chest tubes, and urinary catheters. Imaging studies and other tests to detect bleeding at other sites would have been performed at the discretion of treating clinicians. All available records, including notes from physicians, nurses, and other clinicians, from the first 7 chronologic days of each eligible PICU admission were examined for evidence of clinically significant bleeding.

Clinically significant bleeding was defined as any blood loss or hematoma formation to which the available documentation attributed any of the signs, symptoms, or interventions listed in Box 2.1. These criteria were originally drafted by the principal investigator and the final revised list was developed in consultation with the two senior authors. The principle guiding this definition is that bleeding was considered clinically significant either if it had deleterious effects on the patient (eg. hypotension or death) or if it prompted an unplanned and non-trivial change in management of the patient (eg. transfusion of blood products, use of medications such as antacids to control bleeding, or non-trivial dressing changes or other procedures to control bleeding), without attempting to differentiate clinically significant bleeding of differing levels of severity.

Records were examined until the occurrence of an episode of clinically significant bleeding, discharge from the PICU, or death, whichever came first. Details of the event and its management were recorded for each episode of clinically significant bleeding observed. The time of an episode of clinically

significant bleeding was taken from the documentation describing the episode; if no time was documented for the episode, the time of the documentation itself was assumed to be the time of the episode.

Approximately 10% of charts were randomly selected for independent data abstraction to assess the reliability of data abstraction. Due to the nature of the primary outcome event, it was not possible to blind the assessors to the purpose of the chart review. Charts were examined for evidence of clinically significant bleeding after other data were collected.

Summary statistics were used to describe the demographic and clinical characteristics of patients eligible for this study. Continuous variables were summarized using the mean, median, range, standard deviation, and inter-quartile range. Discrete variables were summarized using frequencies and percentages. The incidence of clinically significant bleeding was determined and a confidence interval (CI) was computed using the Wilson score method. Univariate and multivariate logistic regression were used to calculate odds ratios (OR) and 95% CIs for factors associated with increased risk of clinically significant bleeding. In addition, recursive partitioning, a multivariable technique in which individuals are iteratively separated into groups that are as homogeneous as possible with respect to outcome, was used to classify patients according to bleeding risk. A Kaplan-Meier curve was used to describe the cumulative proportion of patients free of clinically significant bleeding over time.

Box 2.1: Definition of Clinically Significant Bleeding

Clinically Significant Bleeding occurred if blood loss or hematoma formation was observed clinically or with imaging, if this blood loss or hematoma formation was documented in the patient's medical records, and if there was documented attribution to the blood loss or hematoma formation of any of the symptoms, signs, or interventions listed below:

- Death
- Systolic hypotension[a]
- Decrease in hemoglobin concentration of at least 20 g / L from baseline
- Organ dysfunction in any organ system
- Significant symptoms from any organ system
- Cardiopulmonary resuscitation
- Surgical or procedural management of blood loss
- Treatment with volume expanders in volumes of at least 20 mL / kg
- Transfusion of packed red blood cells in any volume
- Use of blood products or medication to control bleeding
- Cessation of anticoagulant medications
- Surgical or procedural investigation of blood loss
- Delay or cancellation of an essential intervention or procedure
- Major revision or reinforcement of a surgical dressing or other dressing

[a] Systolic hypotension was defined as systolic blood pressure less than 90 mmHg for patients aged 10 years or more, less than 70 + 2 x (age in years) mmHg for patients aged 1 year or more but less than 10 years, and less than 70 mmHg for patients aged less than 1 year

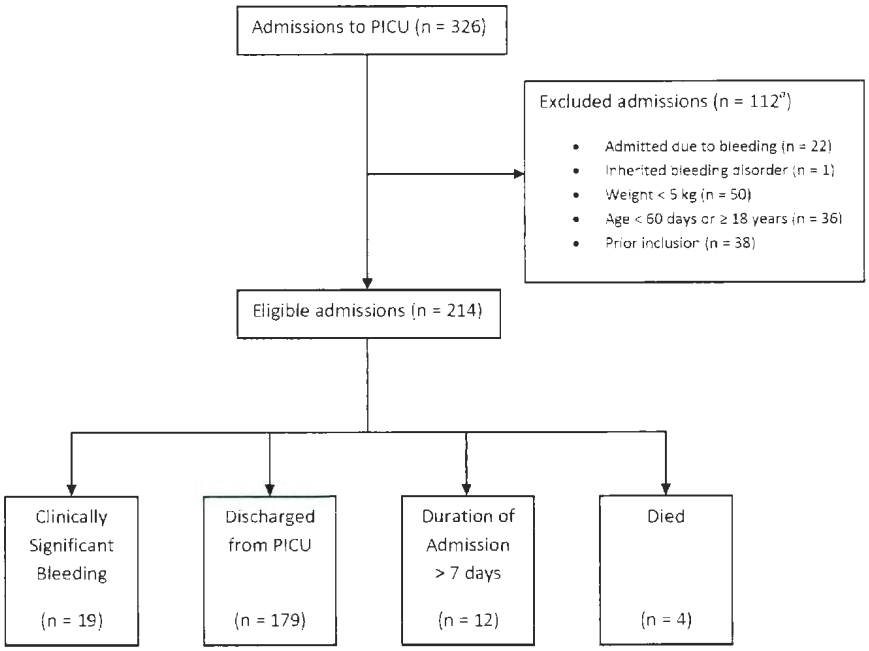
2.3 Results

There were 326 admissions to the PICU during the study period, and 214 were included. The number of patients meeting each exclusion criterion is summarized in Figure 2.1.

Of those 214 eligible admissions, 114 (53.5%) were female. The mean age of included patients was 7.9 years (standard deviation 6.0 years). 94 patients (43.9%) were admitted due to surgery, 118 (55.1%) due to medical conditions, and 2 (0.9%) due to trauma.

There was complete agreement regarding the inclusion and exclusion of admissions (kappa = 1.0), but poor agreement regarding the occurrence of clinically significant bleeding (kappa = 0.26). Consequently, records from all eligible admissions were independently examined by the principal investigator for the occurrence of clinically significant bleeding. Disagreements between the research assistant and principal investigator about whether an episode of clinically significant bleeding had occurred were resolved by one of the senior investigators through examination of patient records and application of the definition in Box 2.1. Episodes of clinically significant bleeding are summarized in Table 2.1.

Figure 2.1: Patients and Outcomes



[a] Some patients met more than one exclusion criterion.

Patient outcomes are shown in Figure 2.1. The incidence of clinically significant bleeding was 8.9% (19 episodes among 214 eligible patients, 95% CI = [5.8%, 13.4%]). Details of these episodes are shown in Table 1. For those patients who experienced an episode of clinically significant bleeding, the median time from admission to the PICU to bleeding event was 9.8 hours (range = [0.5 h, 137.8 h], interquartile range = [4.1 h, 31.6 h]). A Kaplan-Meier analysis of time-to-bleeding-event is shown in Figure 2.3; in this analysis, episodes of clinically significant bleeding were outcome events, and discharge from the PICU and death were censoring events.

A summary of univariate analysis of factors that were considered to be possibly associated with clinically significant bleeding is shown in Table 2.2. Thrombocytopenia (platelet count < 100×10^9 / L, threshold determined from patient data by a recursive partitioning algorithm) was significantly associated with increased odds of clinically significant bleeding. Platelet count was measured in 15 of 19 patients who had clinically significant bleeding, and in 161 of 214 patients overall. Mean platelet counts in the group of patients with clinically significant bleeding (211×10^9 / L, standard deviation 111×10^9 / L) and without (301×10^9 / L, standard deviation 155×10^9 / L) were significantly different ($p = 0.03$).

Table 2.1: Summary of Clinically Significant Bleeding Events

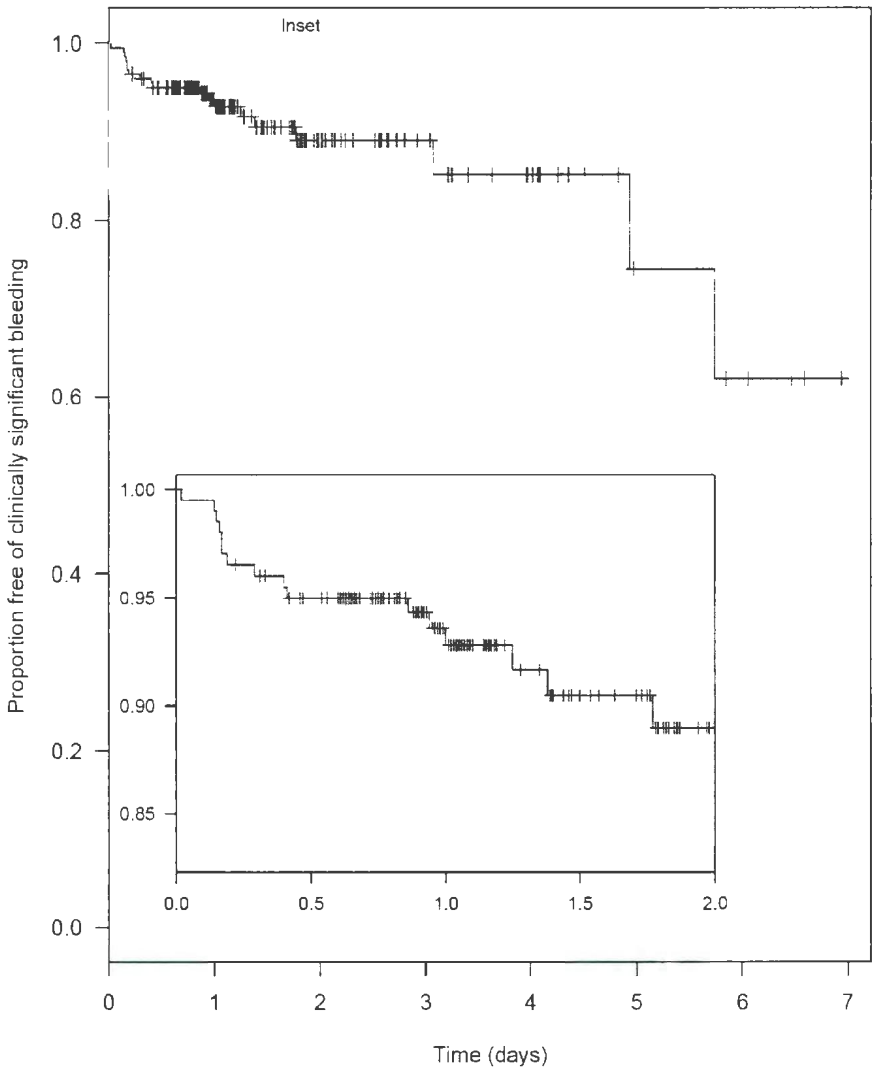
M, male. F, female. y, year. m, month. hr, hour. PICU, Pediatric Intensive Care Unit. PRBCs, Packed Red Blood Cells. FFP, Fresh Frozen Plasma. VSD, Ventricular Septal Defect. NG, Nasogastric tube. G-tube, gastrostomy tube. ECMO, Extracorporeal Membrane Oxygenation. CT, x-ray Computed Tomography. EVD, External Ventricular Drain.

[a] These patients had two different forms of bleeding, both judged to be clinically significant, documented simultaneously in their medical records.

Gender	Age	Reason for Admission to PICU	Time from Admission to Bleeding	Observation of Bleeding	Criteria for Clinically Significant Bleeding
M	15 y 2 m	Congestive heart failure	118.5 hr	bleeding at femoral arterial line site bloody chest tube output[a]	revision of line dressing transfusion of PRBCs, platelets, FFP
F	5 m	Post-op VSD repair	3.6 hr	bloody chest tube output	transfusion of PRBCs, cryoprecipitate, FFP
M	8 m	Post-op VSD repair	22.5 hr	bloody chest tube output	transfusion of PRBCs
M	10 m	Post-op Glen	7.0 hr	nose bleed	epinephrine mask given
F	7 m	Seizures	3.8 hr	blood in NG aspirates	ranitidine given
F	4 y 7 m	Post-op Fontan	3.4 hr	bloody chest tube output	hypotension transfusion of platelets, cryoprecipitate, albumin 5%
M	4 y 11 m	Pneumonia	30.0 hr	blood suctioned from mouth and nose, and vented from G-tube	ranitidine given
F	7 m	Bronchiolitis	9.6 hr	bloody vomitus	NG tube placed
M	10 m	Bronchiolitis	73.6 hr	bloody discharge with removal of NG	ranitidine given
F	13 y 1 m	Seizures	4.1 hr	blood from NG tube	transfusion of platelets stopped NG clobazam
F	5 m	Post-op Glen	33.2 hr	bloody chest tube output	transfusion of PRBCs decrease in hemoglobin by 40 g / L
F	9 y 4 m	Post-op craniotomy	23.9 hr	bleeding through surgical dressing	decrease in hemoglobin by 25 g / L
M	7 y 3 m	Respiratory failure	20.8 hr	bleeding from ECMO catheter site	revision of catheter dressing
M	5 m	Post-op complex cardiovascular surgery	137.8 hr	bleeding from central line site	revision of central line dressing
F	4 y 9 m	Post-op aortic stenosis repair	9.8 hr	bloody chest tube output bloody NG aspirate[a]	decrease in hemoglobin by 47 g / L transfusion of PRBCs, albumin 5% ranitidine given
M	11 y 1 m	Brain tumor	42.5 hr	bleeding from surgical site	revision of surgical dressing
M	3 y 7 m	Post-op VSD repair	4.1 hr	bloody chest tube output	use of volume expanders (normal saline and albumin 5%)
F	14 y 0 m	Post-op Ladd	0.5 hr	surgical dressing soaked with blood	revision of surgical dressing
M	6 y 10 m	Post-op craniotomy and tumour resection	4.5 hr	post-surgical hematoma on head CT	caused abnormal facial movements craniotomy and EVD placed

Figure 2.2: Kaplan-Meier Analysis of Time to Clinically Significant Bleeding Event.

Discharge from the Pediatric Intensive Care Unit (PICU) and death were treated as censoring events, as were stays in the PICU longer than 7 chronological days after admission. The inset figure shows more detail regarding the first 48 hours after admission. Pointwise 95% confidence intervals are shown in grey.


Inset
1.0
0.8
0.6
0.4
0.2
0.0
Proportion free of clinically significant bleeding
1.00
0.95
0.90
0.85
0.0
0.5
1.0
1.5
2.0
0
1
2
3
4
5
6
7
Time (days)

Mechanical ventilation, use of antibiotic and antacid medications, and performance of multiple (3 or more) procedures were among factors that were associated with increased risk as well. Use of antihemostatic medications, prohemostatic medications, and blood products also had significant positive associations with clinically significant bleeding. Use of steroid medication, absence of enteral feeding, INR, and PTT did not.

Given the number of episodes of clinically significant bleeding observed (n = 19), and a published rule-of-thumb that one variable may be included in a multivariate analysis for every ten outcome events observed(15), two variables were chosen for inclusion in a multivariate logistic regression model: mechanical ventilation, which has been previously reported as an important risk factor(6)(5), and thrombocytopenia, which may be an important modifiable risk factor. Both mechanical ventilation (OR 5.6, 95% CI [1.7, 18.5]) and thrombocytopenia (OR 11.8, 95% CI [2.3, 61.2]) were significant risk markers in this multivariate model (Nagelkerke R^2 = 0.23). Anti-hemostatic medications were added to this model: while they had a significant association with increased risk of clinically significant bleeding (OR 4.2, 95% CI [1.1, 15.9]) and thrombocytopenia remained statistically significant (OR 14.3, 95% CI [2.3, 88.0]), mechanical ventilation lost its statistical significance (OR 3.4, 95% CI [0.94, 12.2]) in this model (Nagelkerke R^2 = 0.29). Neither pro-hemostatic medications nor blood products had significant association with bleeding risk when added singly to the original multivariate model.

Table 2.2: Univariate Analysis

CI, confidence interval. INR, International Normalized Ratio. PTT, activated partial thromboplastin time.

Factor	Odds Ratio [95% CI]	p-value
Demographic Variables		
Age (per year)	0.92 [0.84, 1.00]	0.05
Male [a]	1.29 [0.45, 3.78]	0.64
Clinical Variables		
Surgical admission [b]	1.85 [0.65, 5.55]	0.23
Cardiac surgery admission [c]	**7.5 [2.3, 23.9]**	**<0.001**
Mechanical ventilation	**4.5 [1.6, 13.9]**	**0.002**
Enteral feed [d]	1.22 [0.28, 4.14]	0.76
Multiple procedures [e]	**4.2 [1.4, 15.4]**	**0.007**
Antibiotic	**10.9 [1.7, 463.8]**	**0.004**
Antacid	**3.5 [1.2, 10.3]**	**0.01**
Steroid	0.28 [0.03, 1.24]	0.11
Prohemostatic medication	**3.3 [1.1, 9.8]**	**0.03**
Antihemostatic medication	**4.5 [1.6, 13.9]**	**0.002**
Blood product	**3.1 [1.0, 9.1]**	**0.03**
Laboratory Variables		
Platelet count < 100 x 10^9 / L	**12.9 [2.8, 58.8]**	**<0.001**
INR (per unit)	2.2 [0.7, 6.4]	0.15
PTT (per second)	1.00 [0.99, 1.04]	0.34

Factors with statistically significant associations (p-value < 0.05) are in **bold**.
[a] Compared to female. [b] Compared to non-surgical admissions. [c] Compared to all other admissions. [d] Including oral or enteral tube feeds. [e] 3 or more procedures.

When evaluated in patients other than those admitted after cardiac surgery, thrombocytopenia was no longer a statistically significant risk factor (OR 5.1, 95% CI [0.09, 64.0]). There was no interaction between thrombocytopenia and admission following cardiac surgery ($p = 0.99$), and both these factors were significant (cardiac surgery: OR 8.0 with 95% CI [2.4, 26.7], thrombocytopenia: OR 11.2 with 95% CI [2.1, 60.7]) in a main effects multivariate model (Nagelkerke $R^2 = 0.26$).

Since only 3 patients bled after 48 hours or more, we did not feel that the characteristics of such "late bleeders" could be meaningfully analyzed.

2.4 Discussion

This is the first study to apply a broadly inclusive definition of clinically significant bleeding to a group of PICU patients. Others have reported incidences of 1.6%(6) and 5.3%(5) for gastrointestinal tract bleeding in an unrestricted PICU patient population. We found that clinically significant bleeding was more frequent, with an incidence of 8.9%, than was reported by these other studies, likely because of our inclusion of bleeding from all observable sites and of any bleeding that either had deleterious effects on the patient or required changes in patient management.

A prior study found that thrombocytopenia (platelet count less than 100 x 10^9 / L) was associated with significant gastrointestinal hemorrhage in univariate analysis, but not in multivariate analysis(5). Another study of PICU patients defined "coagulopathy" as the presence of a platelet count less than 100 x 10^9 / L or prothrombin time, PTT, or thrombin time greater than 20% above a control

value; patients who met this definition of coagulopathy had an increased risk of clinically significant upper gastrointestinal tract bleeding(6). Importantly, the cut-off values for laboratory tests used in these studies do not appear to have been evidence-based.

We found that a platelet count less than 100×10^9 / L was associated with clinically significant bleeding. This threshold value for predicting bleeding risk has been used in other studies(5,9), but ours is the first study to identify this threshold from patient data. Although a threshold defined from patient data will not be subject to the same biases as a threshold defined by expert opinion (eg. recall bias), a data set derived over a small period of time at a single institution may not produce results that generalize to other settings in which important factors (eg. the proportion of patients admitted for cardiac surgery, the frequency with which a complete blood count is obtained on admission to the PICU, or laboratory instruments) may be different. Furthermore, since we considered only values of platelet count collected near the time of admission, it is possible that this threshold may not apply to platelet counts measured later during an admission.

Although this threshold was no longer had a statistically significant association when patients admitted following cardiac surgery were excluded from the analysis, the 95% CI for the estimated OR was very wide. Therefore, we cannot definitively exclude this degree of thrombocytopenia as a risk marker for clinically significant bleeding in the subgroup of patients who were not admitted following cardiac surgery. A more powerful study will be required to address this.

There is literature in the oncology and hematopoietic stem cell transplantation populations that examines platelet transfusion thresholds. Randomized trials that include some pediatric patients have found no difference in bleeding events using a platelet transfusion threshold of 10×10^9 / L compared to one of 20×10^9 / L(16)(17) or 30×10^9 / L(18). However, these are findings in very specific patient populations and include adult patients: they are not necessarily generalizable to purely pediatric groups or critical care patients. In addition, while these studies do demonstrate that the compared thresholds have equivalent safety, their findings do not imply that the levels of thrombocytopenia considered do not confer a bleeding risk compared to higher platelet counts; nor do they exclude the possibility that a higher transfusion threshold than was examined might reduce the frequency of bleeding events. Indeed, rates of bleeding events in these studies range from 14%(17) to 18%(18)(16), which are higher than we observed. Our result is therefore not inconsistent with these studies.

The lack of evidence-based thresholds for laboratory tests that are used to screen for bleeding risk is one of the major impediments to the development of rational strategies for the use of blood product transfusions and other therapies. However, it would be premature to suggest that critically ill patients should be transfused to maintain a platelet count greater than 100×10^9 / L. Underlying conditions may cause thrombocytopenia and independently cause increased bleeding risk through other mechanisms (e.g. tissue injury, depletion of coagulation factors, decreased platelet function) that might not be corrected by

platelet transfusion.

The use of blood products, pro-hemostatic medications, and anti-hemostatic medications were all found to be risk markers in univariate analysis, but only anti-hemostatic medications remained significant in multivariate analysis. Pro-hemostatic medications and many blood products (eg. platelet concentrates, frozen plasma, cryoprecipitate) might be expected to reduce risk, but their use may be more common in patients who are likely to bleed. The size of our study and the fact that we only considered the use of these medications in a period close to the time of admission, as well as the retrospective nature of our study, prevent us from determining the true role of these therapeutic agents in modifying bleeding risk.

In contrast to platelet count, INR or PTT were unable to predict bleeding risk, as has been previously demonstrated in pediatric patients who have had tonsillectomy/adenoidectomy(4,10,11,19). Although this patient group will have consisted largely of healthy children who differ from PICU patients in many respects – duration of intubation, exposure to medications with possible effects on hemostasis, and presence of medical conditions that may result in impaired hemostasis – it is still a patient group with a known risk of significant bleeding. In this patient group the INR and PTT functioned poorly as predictors of impaired hemostasis, which is in agreement with our findings. It is possible that these tests were not performed sufficiently often in our study population to detect a predictive ability of these tests: platelet count was measured for 161 patients, compared to 85 patients for whom INR and PTT were measured. It may also be

the case that patients who had abnormal INR or PTT on admission to the PICU received treatment to correct these lab values that also decreased bleeding risk. Since we collected only the values for INR and PTT obtained closest to time of admission, we were unable to look for this possible effect.

Our observation that mechanical ventilation is a risk factor for clinically significant bleeding is consistent with other studies(5,6). The finding that use of antibiotic or antacid medications are associated with increased risk of clinically significant bleeding may reflect effects of these medications on hemostasis (e.g. effect of antibiotics on enteric vitamin K metabolism), or may simply reflect bleeding risk conferred by the condition of the patients who received these medications.

Cardiac surgery patients deserve special mention. Eight of 19 episodes of clinically significant bleeding occurred in these patients, and the estimated OR for this group was 7.5. This is not surprising, given the previous observation of high rates of excessive chest tube output in this patient group(1). However we found that 3 of these 8 patients had clinically significant bleeding at other sites. While likely not as serious as blood loss through a chest tube, these other forms of bleeding were sufficient to prompt changes in management. Cardiac surgery patients should be closely monitored for bleeding at sites other than chest tubes.

Ours is the first systematic analysis of the timing of clinically significant bleeding in a general PICU population. Previously available data are limited to surgical patients: patients requiring surgery for idiopathic adolescent scoliosis did not have hemorrhagic complications more than 7 days after surgery(3), and

cardiac surgery patients who had excessive chest tube output did so within 6 hours of PICU admission in 94% of cases(1). In comparison, we found that more than 80% of observed bleeding events occurred within 48 hours of admission to the PICU. Patients may be more likely to experience clinically significant bleeding early during an admission because of factors related to their acute illnesses. In addition, treatment given after admission may rapidly decrease bleeding risk.

Three clinically significant bleeding events were observed in the small group of patients who were admitted longer than 48 hours. Although this would appear to indicate a substantial risk of bleeding for those patients with prolonged admissions, the small patient numbers and wide confidence intervals demonstrated in Figure 2 require caution regarding such interpretation. Specifically, the use of a Kaplan-Meier curve to describe the timing of clinically significant bleeding likely includes an element of informative censoring: nearly all censoring was because of discharge from the PICU, representing clinical improvement that likely indicated decreased bleeding risk for many patients. On the other hand, censoring patients at death is problematic: patients who died may have deteriorated in ways that might actually have increased bleeding risk, but this increased risk would not have been detected. However, it was not possible to estimate this increase in risk with the design of our study.

This study is limited by its retrospective design. In particular, the complex composite definition of clinically significant bleeding that we used resulted in some difficulty with reliable case finding. This was likely due to the difficulty in

ascribing, from chart data only, relevant symptoms or interventions to observed bleeding in a causal manner. However, a study of adult Intensive Care Unit patients has demonstrated that a definition of significant bleeding similar to ours can be reliably applied prospectively(20). Additionally, the time of bleeding was not explicitly documented for some patients, and so for these patients the time of bleeding was assumed to be the time of the documentation of the bleeding. Since an episode of bleeding cannot have occurred *after* its documentation, we may have over-estimated the interval between admission and bleeding in some cases. However, because most bleeding events occurred soon after admission, the effect of this over-estimation is likely small. Observational studies generally cannot establish causation, so the identified risk factors for clinically significant bleeding should be regarded only as associated variables, not causative influences. Because only one episode of clinically significant bleeding could be recorded for each patient, however, the likelihood of spurious associations between patient characteristics and clinically significant bleeding is reduced. A further limitation of our study is the relatively small number of clinically significant bleeding events observed, which limits, in particular, the number of variables included in our multivariate logistic regression models. A larger study in which more bleeding events were observed or a prospective study in which more bleeding events might be captured would provide more detailed multivariate analysis.

2.5 Conclusions

Clinically significant bleeding is more common in the PICU than has been previously reported and the majority of episodes occur in the first 36 hours following admission. The threshold for thrombocytopenia associated with clinically significant bleeding should be confirmed in a prospective study. Other risk markers for clinically significant bleeding include mechanical ventilation, the use of antibiotic and antacid medications, and the performance of multiple procedures.

Chapter 3: A Prospective Study of Common Laboratory Tests of Hemostasis as Predictors of Early Clinically Significant Bleeding in the Pediatric Intensive Care Unit

3.1 Introduction

The pilot retrospective cohort study described in Chapter 2 demonstrated that clinically significant bleeding, defined in a broadly inclusive manner, occurred more frequently in pediatric intensive care unit (PICU) patients than had previously been observed. The large majority of episodes of clinically significant bleeding in the PICU occurred during the first 48 hours of admission. Factors that were observed to be associated with clinically significant bleeding included mechanical ventilation, cardiac surgery, and thrombocytopenia (platelet count less than 100×10^9 / L). This threshold for platelet count has been used before to identify PICU patients presumed to be at increased risk of significant bleeding(5,6,9), but ours was the first study to identify this threshold from analysis of patient data. Other common tests of hemostasis, INR and PTT, were not able to identify patients with increased risk of clinically significant bleeding. However these measurements were made for fewer patients than measurements of platelet count. Furthermore, in that retrospective study we considered these measurements at only one time point, that closest to the time of admission. It is possible then that new information about the ability of platelet count, INR, or PTT to predict clinically significant bleeding could be derived from a study in which more patients were included, more bleeding events were observed, and more

measurements of these quantities were included in the analysis.

We proceeded to a prospective examination of the ability of platelet count, INR, and PTT to predict clinically significant bleeding during the first 72 hours of admission to the PICU, using the same definition of clinically significant bleeding that was used in the pilot retrospective study. Although our broadly inclusive definition of clinically significant bleeding was difficult to apply retrospectively, resulting in some difficulty with case finding, a similar definition has been prospectively applied in adult intensive care unit patients with reliability(20).

3.2 Methodology

This was a prospective observational cohort study conducted in the PICU at the Children's Hospital of Eastern Ontario (CHEO). CHEO is a university-affiliated tertiary care children's hospital with a referral population of approximately 1.5 million people, and the CHEO PICU has 10 beds and an annual average of approximately 600 admissions, including post-operative cardiac surgery patients. Patients are admitted for an average of 3.9 days with an average Pediatric RISk of Mortality (PRISM) score of 5, and 57.4% are mechanically ventilated (CHEO PICU database). This study was approved by CHEO's Research Ethics Board. The Research Ethics Board determined that, because this was a purely observational study, consent from patients or their substitute decision-makers was not required.

A standardized case report form (Appendix 3) and a standardized instruction set for this form (Appendix 4) were developed, and research assistants were trained in their use. Throughout the study period, frequent

communication, both electronically and in person, occurred between the research assistants and the principal investigator to discuss the data collection.

All patients admitted to the PICU during the study period, from January 4th 2010 to August 20th 2010, were considered for inclusion in this study. Criteria for exclusion were prior inclusion in this study, previous diagnosis of an inherited bleeding disorder, admission to the PICU because of bleeding, age at admission less than 60 days or greater than or equal to 18 years, and weight at admission less than 3 kg. These are the same exclusion criteria that were used in the pilot retrospective study, with the exception of the lower limit for weight, which had been 5 kg. This change was made because it was felt, after the completion of the retrospective study, that some patients had been excluded solely because of this higher weight limit but did not have a history of prematurity or other characteristics that might have differentiated them from the general study population in terms of the risk of serious bleeding such as intracranial hemorrhage.

The paper and electronic medical records of all included patients were examined to extract each patient's age, gender, weight, reason for admission, and time of admission. Each included patient's admission was divided into consecutive 24 hour time periods from 24 hours prior to admission to 72 hours after admission, and the following information was extracted for each time period: maximum and minimum vital signs (heart rate, respiratory rate, systolic blood pressure, oxygen saturation, and temperature); use of supplementary oxygen, mechanical ventilation, and enteral or parenteral feeds; medications (antibiotics,

antacids, steroids, pro-hemostatics, anti-hemostatics), blood products, and procedures. The results of all measurements of platelet count, INR, PTT, and plasma fibrinogen concentration, as well as the dates and times of these measurements, were recorded. The dates and times of administration of platelet concentrates, frozen plasma, cryoprecipitate, and vitamin K were also recorded.

The primary endpoint for the study was clinically significant bleeding. Bleeding was considered to be clinically significant bleeding if and only if it satisfied, in the opinion of bedside caregivers, any of the criteria described in Box 2.1. Blood loss or hematoma formation at any site was considered, with one exception: because the retrospective study demonstrated a very high incidence of excessive chest tube bleeding among cardiac surgery patients and because this form of bleeding was essentially limited exclusively to cardiac surgery patients, excessive chest tube bleeding in cardiac surgery patients, while it was recorded, was not included in the analysis; bleeding from other sites in cardiac surgery patients could be included if it satisfied any of the criteria in Box 2.1.

In order to detect episodes of clinically significant bleeding, bedside nurses and physicians (including trainees such as residents and fellows) in the PICU were contacted daily. This communication was usually in the form of visits to the PICU, but on the weekends or on holidays it may have taken place over the phone. During these communications, these bedside caregivers were asked whether patients included in the study had experienced any bleeding or hematoma formation. In the event that bleeding or hematoma formation had occurred, bedside caregivers were then asked whether the patient satisfied any

of the criteria in Box 2.1. Finally, if any of these criteria were satisfied, bedside caregivers were asked if the observed blood loss or hematoma formation was the cause of observed signs or symptoms or the reason for any interventions. A printed sheet (Appendix 5) was used to identify these criteria for bedside caregivers. The time of a clinically significant bleeding event was given by bedside caregivers, taken from documentation describing the event, or assumed to be the same as the time of the documentation describing the event.

For reasons of practicality and availability of data collectors, repeated independent data collection, for purposes of assessing the reliability of both data collection and detection of clinically significant bleeding events, was not done for any patients.

This was a purely observational study, and no specific protocol for clinical, laboratory, or radiographic monitoring was required. The study did not mandate any interventions for patients who had abnormal blood test results or other characteristics that might have been thought to increase bleeding risk. Patients were assumed to receive standard care and monitoring in the PICU. Interventions were solely at the discretion of bedside caregivers.

Data collection for each included patient continued until the patient was discharged from the PICU or died, or until 72 hours after admission, whichever came first.

Descriptive statistics were used to describe patient demographics and the overall incidence of clinically significant bleeding. A Kaplan-Meier curve was used to describe time from admission to clinically significant bleeding events.

Univariate Cox proportional hazard models were constructed using some fixed covariates such as admission diagnosis, and measurements of platelet count, INR, PTT, and fibrinogen as time-varying covariates(21). The last measured value of one of these quantities was used until a new measurement was made. In order to include those patients for whom these measurements were not available at given time points and to account for the effects of transfusion of platelets, frozen plasma, and cryoprecipitate, the Cox proportional hazard analysis was repeated, using the following rules to generated imputed values of platelet count, INR, PTT, and fibrinogen: (1) Platelet transfusion was assumed to raise the platelet count by 50×10^9 / L, following expert opinion in the literature(22). (2) Transfusion of frozen plasma was assumed to restore the PTT and INR to the upper limit of the age-dependent reference ranges in the CHEO laboratory. (There are no algorithms or opinions to estimate the effects of plasma transfusion on these parameters.) (3) Transfusion of cryoprecipitate was assumed to restore the fibrinogen level to the lower limit of the age-dependent reference range in the CHEO laboratory. (Again, no literature describes estimated effects of cryoprecipitate transfusion.) (4) If no measurement of platelet count, PTT, INR, or fibrinogen had yet been made for a patient, the value of that quantity was assumed to be the midpoint of the age-dependent reference range for that quantity in the CHEO laboratory. In the case of patients for whom a quantity was never measured, this midpoint value is assumed throughout their inclusion in the study. This rule is based on an assumption that clinician behaviour is informative: if these measurements had not been made before a

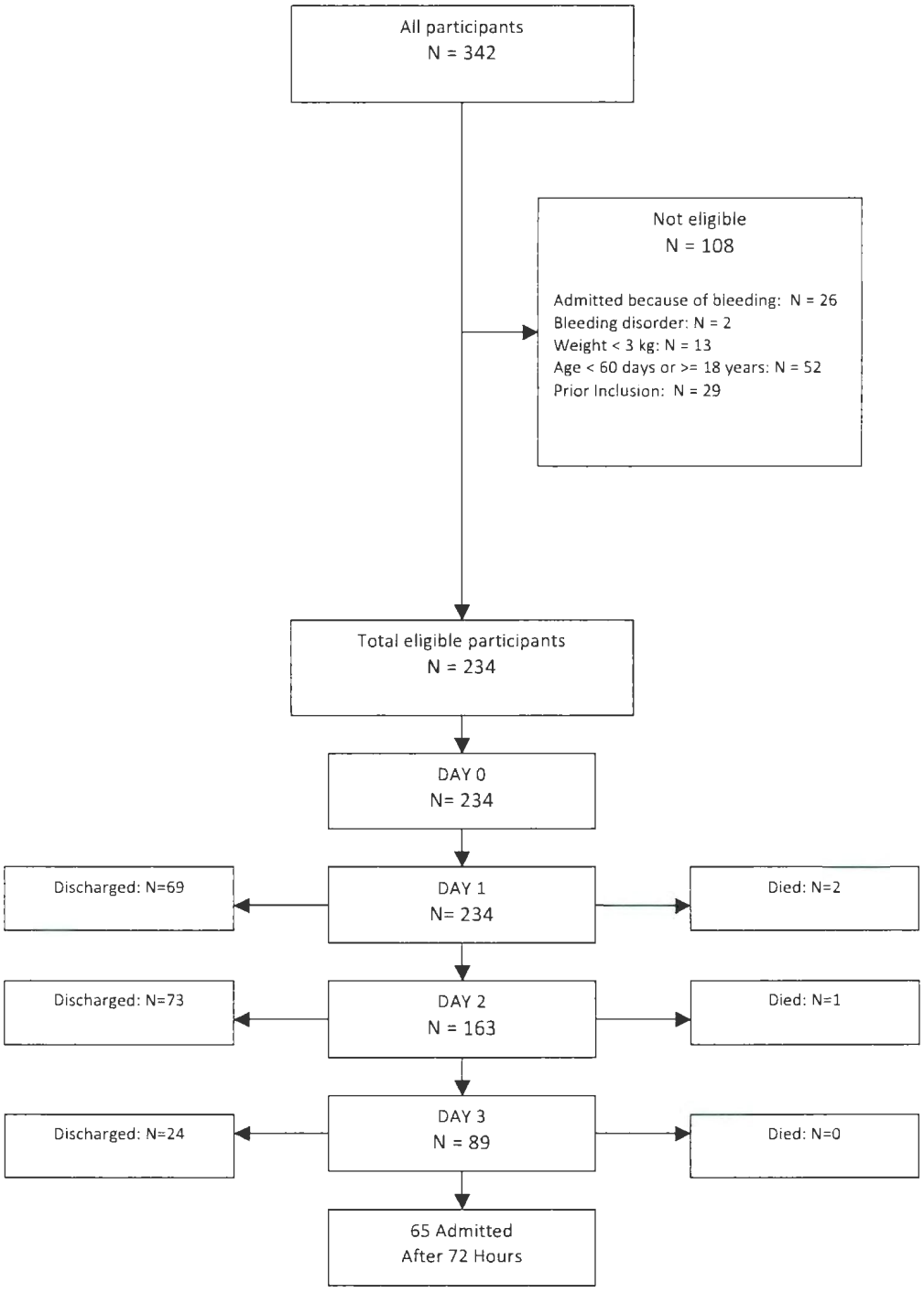
particular time, treating clinicians likely believed, based on clinical information about the patient, that the results of these tests would have been normal. Because vitamin K administration does not immediately correct the INR and because virtually all patients who received vitamin K had their INR rechecked within 24 hours, it was not necessary to use imputed corrections for INR after vitamin K administration and the effect of vitamin K was not analyzed.

In these analyses, censoring patients at discharge from the PICU is likely informative: patients who were discharged had clinically improved in ways that, in many cases, likely decreased their bleeding risk. In order to explore this possible effect, the Cox analyses were done with both this censoring rule and without. In the latter analysis, even though no further data were collected on patients who had been discharged from the PICU, they were assumed to have no bleeding risk after discharge. Deaths were treated as censoring events in both analyses.

3.3 Results

During the study period, 342 patients were admitted to the PICU. 40 charts (11.7%) were selected at random for independent re-entry of data from the case report forms to the database. The rate of discrepancies between the two data entries was 0.37%, less than the 0.5% that had been pre-determined as the maximum acceptable error rate for the data entry. The error rate for data items related to the occurrence of bleeding events and to measurements of platelet count, INR, PTT, and fibrinogen was 0.1%.

Figure 3.1: Patients and Outcomes



The flow of patients through the study is shown in Figure 3.1. Of the 342 patients admitted to the PICU during the study period, 108 were ineligible: 27 were admitted to the PICU because of bleeding; 2 had a previously-diagnosed inherited bleeding disorder; 13 weighed less than 3 kilograms; 52 were less than 60 days of age or greater than or equal to 18 years of age; and 29 had been included in the study during a prior admission to the PICU. (Some patients met more than one exclusion criterion.) The remaining 234 patients were included in the study. The numbers of eligible patients still being followed 24, 48, and 72 hours after admission were 163, 89, and 65, respectively. The cumulative number of deaths 24, 48, and 72 hours after admission were 2, 3, and 3, respectively.

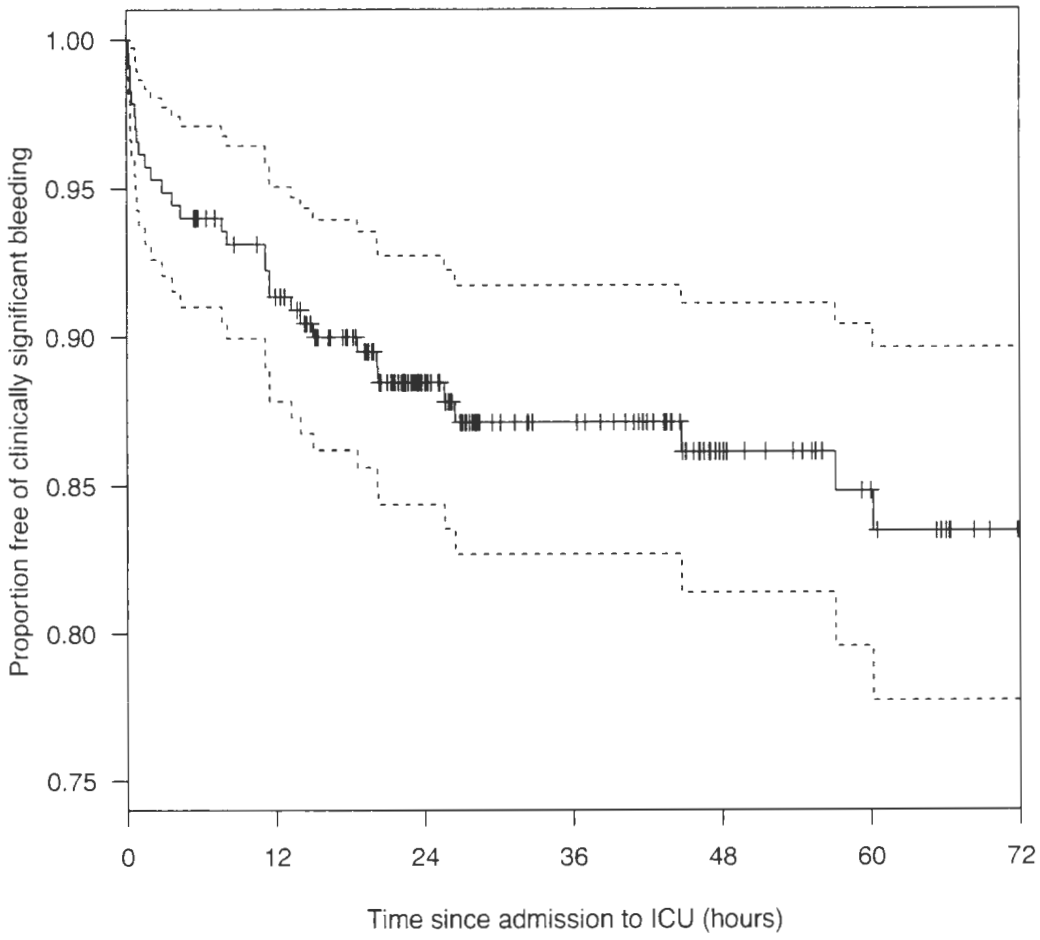
109 included patients (46.6%) were female. Median patient age at time of admission was 62 months (range 2 to 215 months, inter-quartile range 144 months), and median patient weight was 18 kilograms (range 3.1 to 107 kilograms, inter-quartile range 37.5 kilograms).

5 eligible patients (2.1%) were admitted to the PICU because of trauma, 111 (47.4%) were admitted following surgery, and 118 (50.4%) were admitted because of medical illnesses.

Overall, 31 patients (13%) experienced one or more episodes of clinically significant bleeding during the first 72 hours of admission to the PICU. 21 patients had a single episode of clinically significant bleeding, 8 had two episodes, and 2 had three episodes.

Figure 3.2: Kaplan-Meier Analysis of Time to Clinically Significant Bleeding Event.

95% confidence intervals shown in dashed lines.



A Kaplan-Meier analysis of time to clinically significant bleeding event is shown in Figure 3.2.

There were 22 eligible patients in the study who had no laboratory evaluation of hemostasis during their inclusion in the study, and none of these patients experienced episodes of clinically significant bleeding. This provides conceptual validation for the imputation rule that assumed values of INR, PTT, and fibrinogen at the mid-point of the age-appropriate normal range for patients for whom these measurements had not been made.

There were 21 patients who received one or more platelet transfusions, 9 patients who received one or more transfusions of cryoprecipitate, and 11 patients who received one or more transfusions of FFP.

In Cox proportional hazard models using platelet count, INR, PTT, and fibrinogen as univariate time-varying covariates, with use of the imputation rules described above and with discharge treated as a censoring event, only platelet count had a statistically significant association with clinically significant bleeding (HR = 0.67 per 100 x 10^9 / L increase in platelet count, 95% CI = 0.49 – 0.92, p = 0.01). When these analyses were repeated with discharge not considered a censoring event and with the assumption that clinically significant bleeding did not occur after discharge, platelet count was again the only parameter with a statistically significant association with clinically significant bleeding (HR = 0.66 per 100 x 10^9 / L increase, 95% CI = 0.48 – 0.90, p = 0.01).

Table 3.1: Hazard Ratios for Clinically Significant Bleeding, from a Multivariate Model, with and without Censoring at Discharge

	Discharge times treated as censored observations		Discharged patients assumed to have no further bleeding	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Platelet count (per increase by 100 x 10^9 / L)	0.68 (0.49, 0.93)	0.02	0.67 (0.49, 0.92)	0.01
INR (per increase in numerical value by 1)	0.96 (0.44, 2.07)	0.92	0.97 (0.47, 2.03)	0.94
PTT (per increase by 1 second)	1.00 (0.98, 1.03)	0.76	1.01 (0.98, 1.03)	0.73
Fibrinogen (per increase per 1 g / L)	1.03 (0.83, 1.27)	0.78	1.04 (0.85, 1.28)	0.70

Results from Cox proportional hazards models using platelet count, INR, PTT, and fibrinogen as multiple time-varying covariates, both with and without censoring at discharge from the PICU, are shown in Table 3.1.

In order to further explore the relationship of platelet count with clinically significant bleeding, and to attempt to identify a threshold of platelet count that might be of clinical use, the Cox proportional hazard model was reconstructed using a discretized variable based on platelet count: the variable had a value of 1 if the platelet count was greater than or equal to a threshold value, and 0 if the platelet count was less than the threshold value. Figure 3.3 shows the HRs for clinically significant bleeding at various threshold values for platelet count based on Cox proportional hazard models with only platelet count as a time-varying covariate. Figure 3.4 shows the results of this analysis when repeated with Cox proportional hazard models that included INR, PTT, and fibrinogen as well as platelet count as time varying-covariates.

Clinical variables were selected, from among those identified as potential risk markers in the retrospective study, for inclusion in models examining the association of platelet count with clinically significant bleeding. (Because there was no suggestion in univariate models of any association between INR, PTT, or fibrinogen concentration with clinically significant bleeding, these variables were not re-examined in expanded multivariate models.) A causative association between thrombocytopenia and clinically significant bleeding is biologically plausible. For this reason, a multivariate model was constructed specifically to explore the ability of platelet count to explain clinically significant bleeding, rather

Figure 3.3: Hazard Ratios for Clinically Significant Bleeding for Patients with Platelet Counts Above or Below Various Thresholds

Hazard ratios (on the vertical axis) for clinically significant bleeding are for patients whose platelet count is less than the threshold value given by the position on the horizontal axis, compared to patients whose platelet count is greater than that threshold value.

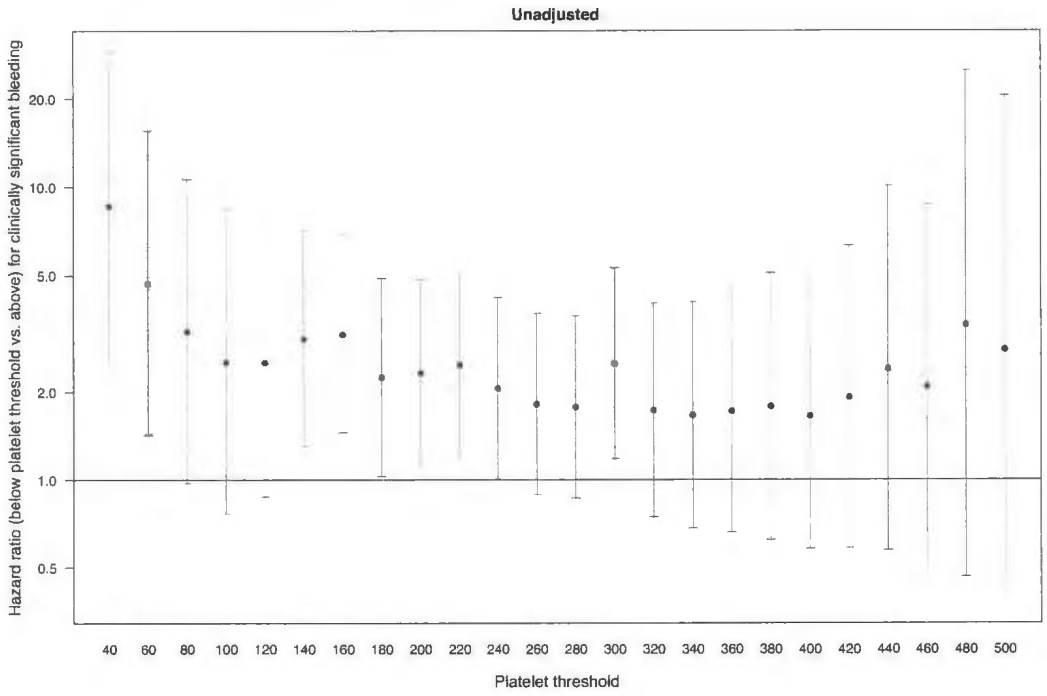
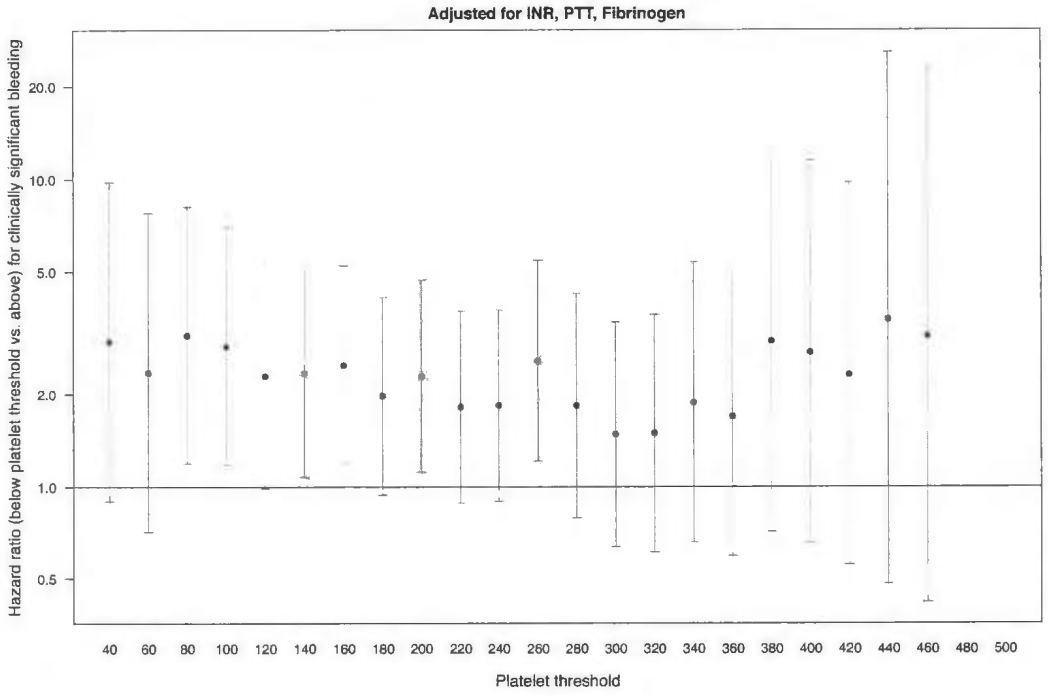


Figure 3.4: Hazard Ratios for Clinically Significant Bleeding for Patients with Platelet Counts Above or Below Various Thresholds, with Adjustment for INR, PTT, and Fibrinogen Concentration

Hazard ratios (on the vertical axis) for clinically significant bleeding are for patients whose platelet count is less than the threshold value given by the position on the horizontal axis, compared to patients whose platelet count is greater than that threshold value.



than to try to construct the best predictive model(23).

To this end, clinical risk markers were identified that were potential confounders for platelet count: variables that might have both an association with platelet count and an association with clinically significant bleeding independent of the relationship with platelet count. Considering the clinical risk markers examined in the retrospective study, potential confounders of platelet count were: admission for cardiovascular surgery (n = 26 patients), which is associated with thrombocytopenia and which may increase bleeding risk through derangements of other components of hemostasis as well; admission for infection (n = 48), because infections can cause thrombocytopenia and may also cause consumptive coagulopathies that could increase bleeding risk; use of antibiotics (n = 81), which are among the medications most commonly implicated in medication-associated thrombocytopenia(24) and can also decrease coagulation factor levels by inducing abnormalities of vitamin K metabolism; and use of unfractionated heparin (UFH) (n = 31), which directly antagonizes some coagulation factors and can decrease platelet count through an immunologic mechanism (heparin-induced thrombocytopenia [HIT]) that can occur in pediatric patients(25). These were all identified as risk markers in the retrospective study, with the exception of admission for infection. (There was no effect of admission diagnosis except for those patients admitted for cardiac surgery, and specific medical diagnoses, such as infection, were not considered separately.) However, this variable was considered a potentially important confounder.

Clinical variables that were identified as risk markers in the retrospective

study but were not included in the analysis here include mechanical ventilation (there is no direct mechanism by which this might affect platelet count) and use of antacid medications (which are likely less common causes of thrombocytopenia than are antibiotics(24)). Low molecular weight heparin (LMWH) is a less common cause of HIT(25) than UFH and was used in only 7 patients, so LMWH heparin was not included. Admission for trauma could possibly be a confounder, but only 5 patients had this admission diagnosis, and so this was not included. The existence of unknown confounding variables cannot be excluded.

Since there were only 31 patients who experienced clinically significant bleeding, we sought to reduce the number of variables analyzed by examining correlations between variables using Fisher's exact test. Admission for cardiac surgery was strongly correlated with both UFH use (95% CI for OR = [42, 1131], $p << 0.001$) and antibiotic use (95% CI for OR = [4.4, 57], $p << 0.001$) at any time during the period of data collection. Admission for infection was also correlated with antibiotic use (95% CI for OR = [1.3, 5.7], $p = 0.002$). Given these associations, the time-invariant variables admission for cardiac surgery and admission for infection were selected for inclusion in a multivariate model.

In a Cox proportional hazards model including platelet count as a time-varying covariate and admission for cardiac surgery and admission for infection as time-invariant covariates, the association between platelet count and clinically significant bleeding was of borderline statistical significance (HR = 0.72 per increase in platelet count of 100×10^9 / L, 95% CI = [0.516, 1], $p = 0.0497$); admission for cardiac surgery had a significant association (HR = 2.68, 95% CI =

[1.14, 6.29], p = 0.023) and admission for infection did not (HR = 0.80, 95% CI = [0.292, 2.21], p = 0.67)

3.4 Discussion

This is the first prospective study of clinically significant bleeding in the PICU that attempted to capture clinically significant bleeding at all possible anatomic sites (except excessive chest tube bleeding in cardiac surgery patients). Using this approach, we found that the incidence of clinically significant bleeding in the first 72 hours of PICU admission was 13%. This is higher than the incidence in our retrospective study (Chapter 2), and is also higher than any incidence reported in other published literature(5,6).

Given the difficulty in reliably identifying cases of clinically significant bleeding retrospectively, it is likely that prospective study results in a higher incidence because of improved case-finding. It appears that case-finding can be improved through prospective study, so that any further investigations of clinically significant bleeding in the PICU should be conducted prospectively. The results of studies conducted retrospectively should be interpreted with caution.

Of particular interest is the comparison between the Kaplan-Meier curves in Figures 2.1 and 3.2. The former demonstrates a "shoulder" just after the time of admission, during which time few clinically significant bleeding events were observed; this "shoulder" is absent in the latter curve. While this difference may simply be due to chance, it is also possible that it demonstrates a difficulty in reliably documenting bleeding during the typically busy time around a patient's admission to the PICU, further supporting the notion that bleeding in PICU

patients should be studied prospectively.

In order to reliably capture bleeding events near the time of admission, one approach might be to institute formalized bleeding assessment as part of the routine of admission. Tools adapted from those of Arnold et al.(20) or the Neonatal Bleeding Assessment Tool (NeoBAT)(26) could easily be incorporated into routine admission documentation. This may improve the detection of clinically significant bleeding events near the time of admission, although this assertion would have to be proven systematically.

The incidence of clinically significant bleeding we report here is considerably higher than other reports, which only consider bleeding at specific anatomic sites(5–7). Our results demonstrate that this limited approach underestimates the scope of bleeding as a clinical problem in PICU patients.

Ten patients (32% of the patients with clinically significant bleeding, 4% of all included patients) had more than one episode of clinically significant bleeding. Analysis of the characteristics of these repeat bleeders has been deferred.

The timing of clinically significant bleeding in the PICU is described in Figure 3.2. Clinically significant bleeding occurs most often early during an admission to the PICU, with the Kaplan-Meier curve showing evidence of "flattening" as time goes on. As in the pilot retrospective study, it is difficult to comment on bleeding risk for patients admitted to the PICU longer than 48 hours, because of small patient numbers and wide confidence intervals on the Kaplan-Meier curve.

The most important part of our analysis involves commonly-used

laboratory tests of hemostasis such as platelet count, INR, PTT, and fibrinogen concentration. Of these, only platelet count had a statistically significant association with clinically significant bleeding. This association persisted, with a p-value bordering on 0.05, after inclusion of potentially confounding clinical variables (admission for cardiac surgery and admission for infection) in the model. Unfortunately, the number of observed episodes of clinically significant bleeding limited the number of variables that could be included in the model. Cardiac surgery has a strong association with clinically significant bleeding (9 patients out of 26 admitted after cardiac surgery had episodes of clinically significant bleeding), and likely confounds the association between platelet count and clinically significant bleeding to some extent. However, the results obtained in this study suggest that reductions in platelet count do influence bleeding risk independently of this factor.

One possible explanation for the observed association with platelet count and lack of association with INR and PTT is that perhaps platelet count is the only one of these laboratory parameters that actually is associated with clinically significant bleeding. Platelets have a number of functions in hemostasis, including adhesion and aggregation during formation of the initial platelet plug, as well as providing the surface on which the coagulation cascade is activated, ultimately forming of a cross-linked fibrin mesh(27). Thrombocytopenia might then be expected to result in significant impairment of hemostasis. An effect of thrombocytopenia on fibrin formation would be undetected by the PTT and INR, as these tests are performed with plasma rather than whole blood, with acellular

substitutes for the phospholipid membrane of platelets.

PTT and INR, on the other hand, measure only the function of coagulation factors. Furthermore, they are not equally sensitive to all coagulation factors. The INR, for example is very sensitive to factor VII, which makes it a useful test for monitoring the effects of coumarin vitamin K antagonists(28). These tests were not designed as tests of global hemostatic potential, and there are no data to support their use in this manner in general populations of pediatric patients. Fibrinogen, while an important part of coagulation, is only a single factor, and so is likewise not a test of global hemostatic potential. Furthermore, congenital fibrinogen deficiency has an extremely variable clinical phenotype, including some patients with minimal bleeding symptoms(29), suggesting that fibrinogen concentration alone does not predict bleeding.

Another possible explanation of our failure to observe an association between INR, PTT, or fibrinogen concentration and clinically significant bleeding is that these tests were performed less often than was measurement of the platelet count: platelet count was measured an average of 1.23 times per 24 eligible patient-hours, compared to 0.58 times for INR and PTT and 0.57 times for fibrinogen concentration. A larger study, a study in which these latter measurements were made more frequently, or a study in which these measurements were made in a systematic rather than an *ad hoc* manner might detect an effect that was not seen here.

We explored the association of different threshold values for platelet count with clinically significant bleeding. Although estimated hazard ratios greater than

1 were seen for all platelet count thresholds, these were only statistically significant at lower thresholds (less than 240 x 10^9 / L). Even at some lower thresholds, wide confidence intervals prevented estimated hazard ratios from being considered statistically significant.

Estimated hazard ratios do appear to increase at thresholds below 100 x 10^9 / L. However an increase in hazard ratios for lower thresholds of platelet count was not seen in models incorporating INR, PTT, and fibrinogen concentration were included as additional time-varying covariates. Although these tests lacked predictive ability on their own, it is conceivable that coagulation factor deficiencies identified by these tests might have predictive value in the setting of thrombocytopenia. A larger study that included more patients with significant thrombocytopenia would be needed to investigate this further.

Our retrospective study identified a threshold for platelet count (less than 100 x 10^9 / L) that was associated with clinically significant bleeding. This same threshold was not identified in this prospective study. Reasons for this may include differences in study design (eg. duration of data collection or the number of measurements of platelet count that were included in the data set), study data (eg. a higher incidence of clinically significant bleeding was seen in the prospective study), or analytic technique (logistic regression vs. Cox proportional hazards models). It may be the case that, despite the clinical utility of cutoff values, there does not exist a cutoff value for platelet count that clearly discriminates between patients with high and low bleeding risks. In this case, the identification of a cutoff value in the retrospective study may simply have been an

artifact of an inherently limited data collection.

Ultimately our work would be of most interest if it could motivate change in the management of PICU patients who were at risk of clinically significant bleeding. Based on our results, correction of thrombocytopenia through platelet transfusion might seem a sensible strategy. However, the correct circumstances under which to do this are not clear. The hazard ratios shown in Figure 3.3 suggest that a platelet count below 60 x 10^9 / L might be appropriate, but the exploratory analysis used to produce this figure should not be considered conclusive. Furthermore, it should not be assumed that, because thrombocytopenia is a risk marker for clinically significant bleeding, correction of thrombocytopenia would ameliorate bleeding risk. An experimental clinical study would be the only way to prove the utility of platelet transfusion for thrombocytopenic patients in the PICU.

3.5 Conclusions

Prospective detection of clinically significant bleeding in pediatric intensive care unit patients demonstrates that clinically significant bleeding is more common than previously reported. Clinically significant bleeding is a complication most often seen early in an admission to the PICU. Platelet count is associated with clinically significant bleeding, but INR, PTT, and fibrinogen concentration are not. More extreme thrombocytopenia may be associated with greater hazard of clinically significant bleeding. Our results provide sufficient rationale to justify an experimental evaluation of platelet transfusion to prevent bleeding complications in selected PICU patients with severe thrombocytopenia.

Chapter 4: Summary and Conclusions

4.1 Incidence of Clinically Significant Bleeding in the PICU

Our results, from both the retrospective and prospective studies, demonstrate that clinically significant bleeding is more common among PICU patients than had been reported by previous studies that considered only bleeding from a specific site such as the gastrointestinal tract.

Furthermore, we observed a higher incidence of clinically significant bleeding in the prospective study than in the retrospective study. This demonstrates that significant bleeding events are not reliably captured by medical records alone; this may be particularly true early in an admission to the PICU. In addition, the poor agreement between chart abstractors in identifying bleeding events in the retrospective study shows that events, even when documented in the medical record, may be difficult to recover retrospectively. Because of this, prospective observation should be required in any further studies of bleeding in PICU patients.

In both the retrospective and prospective studies, we did not follow patients after discharge from the PICU, and cannot comment on the incidence of clinically significant bleeding post-discharge. It is likely that patients would have decreased bleeding risk after discharge, for a number of reasons: more advanced wound healing for surgical patients, less exposure to medications that might alter hemostasis, being subject to fewer invasive procedures, and improvement of conditions that cause thrombocytopenia, consumptive coagulopathy, or other

acquired causes of impaired hemostasis. However, there may be a risk of post-discharge bleeding for some patients, which may be severe enough to require re-admission to the PICU in some cases. The characteristics of such patients would have to be determined in a separate prospective study.

In our prospective study, we did record multiple bleeding events for 10 patients (32% of patients who had clinically significant bleeding events, and 4% of all patients). Since data collection in the retrospective study stopped with a clinically significant bleeding event, we have no estimate of the incidence of recurrent events from this study; however, it is to be expected that prospective data collection would provide a more accurate estimate of the incidence of this phenomenon. Determination of the characteristics of this group of repeat bleeders has been deferred.

4.2 Timing of Clinically Significant Bleeding in the PICU

Our pilot retrospective study is the first systematic examination of the timing of clinically significant bleeding among PICU patients. We found that more than 80% of episodes of clinically significant bleeding occurred within 48 hours of admission. Owing to small numbers of patients whose admissions lasted longer than 48 hours, it was not possible to conclude whether bleeding risk declines significantly over time for patients with prolonged admissions.

In spite of this, it is reasonable to suggest that patients be closely observed for the occurrence of bleeding early during their admissions. Since our prospective study only followed patients to a maximum of 72 hours after admission to the PICU, it contributes no information to a discussion of bleeding

risk for patients with prolonged PICU admissions.

4.3 Clinical Risk Markers for Clinically Significant Bleeding

Our retrospective study identified a number of clinical risk markers for clinically significant bleeding, including some that are theoretically modifiable (thrombocytopenia, mechanical ventilation, antibiotic and antacid medications, multiple procedures) and some that are not (cardiac surgery, for example). Treatment-related risk markers, however, might not be modifiable in practice. For example, a patient might require mechanical ventilation in spite of a perceived bleeding risk associated with this therapy.

Because only a small number of clinically significant bleeding events were observed in the retrospective study, it was not possible to simultaneously evaluate many clinical risk markers in a multivariate logistic regression model. Consequently, we cannot comment on whether these are all independent risk markers. It may be the case that some of these variables are correlated with one another and that their associations with bleeding risk are not, therefore, independent of one another.

The prospective study was designed specifically to examine the association between laboratory tests of hemostasis and clinically significant bleeding. However, analysis of clinical variables was performed in a multivariate model including platelet count: admission for cardiac surgery was significantly associated with clinically significant bleeding, and admission for infection was not. However, the number of clinical variables analyzed was limited by the number of observed episodes of clinically significant bleeding. Our prospective study was

deigned primarily to examine laboratory variables, and it is possible that important clinical variables were not examined.

An important use for observed clinical risk markers is to identify patients who are at increased risk so that they can be monitored closely for bleeding complications. Our work helps to identify such patients. However, appropriate interventions to reduce bleeding risk in patients with these risk markers remain to be identified.

4.4 Laboratory Risk Markers for Clinically Significant Bleeding

In both the retrospective and prospective studies, platelet count was seen to have an association with clinically significant bleeding. INR, PTT, and fibrinogen concentration did not. In the prospective study, this was in spite of a more sophisticated and thorough analysis that included measurements at multiple time points (when available) and imputed corrections following transfusion of hemostatically active blood products.

An exploratory analysis of platelet counts in the prospective study identified 60×10^9 / L as a threshold that might be of interest: this is the threshold below which the hazard ratio for clinically significant bleeding appeared to increase.

The possible reasons for the lack of association of other tests with clinically significant bleeding were discussed in Chapter 3. In the end, either these tests do not have predictive ability at all or these tests are not sufficiently strong risk markers to have been identified by our studies. In either case, INR, PTT, and fibrinogen concentration should not be considered to be strong

predictors of hemorrhagic risk.

The use of laboratory tests that have not been demonstrated to possess predictive value carries potential risks. Abnormal values of these tests may prompt interventions that, while they may correct the abnormal test result, might not reduce bleeding risk. These interventions involve exposure to blood products, which can cause acute transfusion reactions(30) and transfusion-associated acute lung injury(31). In the face of these known risks, it is questionable to apply interventions of unknown efficacy.

4.5 Limitations

Our pilot study had limitations typical of retrospective studies; these limitations have already been discussed at length in Chapter 2. The most significant of these limitations was the difficulty in identifying cases of clinically significant bleeding. Comparison of our two studies suggests that bleeding episodes that occur very shortly after admission to the PICU might be particularly difficult to identify from medical records alone. The clear lesson is that clinically significant bleeding cannot be reliably identified solely from medical records. Prospective identification of clinically significant bleeding, using a broadly-inclusive definition similar to the one used in our studies, does appear to be reliable(20). We do not, therefore, expect that the results of our prospective study will have been biased by the omission of a particular subset of bleeding episodes. However, the reliability of our definition of clinically significant bleeding in prospective data collection was, for practical reasons, not assessed and should be confirmed in a subsequent study.

Criticism of our studies may be directed at our definition of clinically significant bleeding. The likely forms of these criticisms will be either that there is subjectivity involved in our definition or that our definition does not differentiate between bleeding events of differing severity. Both of these points are true, but these are not, in fact, significant limitations of our definition of clinically significant bleeding.

There is subjective assessment involved in our definition of clinically significant bleeding events. This subjectivity takes two forms: the attribution of signs, symptoms, or interventions to bleeding; and the decision to perform interventions in response to bleeding. But it is not clear that more objective criteria for defining significant bleeding would be more useful.

The most objective possible criterion, for example, would be the volume of blood loss. In post-operative pediatric cardiac surgery patients, it is possible to directly measure the volume of blood loss through chest tubes, and this has been used to classify some bleeding as excessive(1,2). However, the volume of chest tube bleeding that is considered excessive is itself subjectively defined, which is to say defined according to the subjective judgement of other investigators. Furthermore, such precise quantitative measurements of blood loss are not possible in most other patients. Even more complexity is added when one considers bleeding in different sites. A volume of bleeding that might be of minor concern in one site, such as the gastrointestinal tract, may be catastrophic in another, such as the intracranial space. These points demonstrate that the most objective possible method for gauging the severity of bleeding, measurement of

the volume of bleeding, is of little practical use.

There are no evidence-based systems of classification of bleeding according to whether specific intervention is required. (The lack of such algorithms was one of the motivations for our studies.) In this circumstance, relying on the judgement of treating physicians to contribute to the identification bleeding that requires intervention is reasonable and not without precedent. Physician judgement has been successfully incorporated, for example, into clinical decision rules for identifying patients who require imaging to detect deep vein thromboses(32) and pulmonary emboli(33).

It is also true that our definition does not differentiate between bleeding of different severities, as long as one or more criteria for clinically significant bleeding are met. There are available grading systems for bleeding, such as the World Health Organization (WHO) classification(34) and the Buchanan system for grading bleeding associated with immune thrombocytopenic purpura(35), but these systems are semi-quantitative and somewhat arbitrarily-defined. Furthermore, it has not been established that such classifications are of any practical use in guiding management or indicating prognosis. There is, therefore, no rationale for attempting to subdivide bleeding events according to severity.

Both of the studies we performed were purely observational, and as a result cannot definitively establish causation between putative risk markers and clinically significant bleeding. We cannot, therefore, recommend any interventions to decrease bleeding risk, based on our studies.

4.6 Significance and Further Directions

Our results provide the most complete and sophisticated description and analysis of clinically significant bleeding in the PICU to date. The pilot retrospective study identified clinical risk markers for clinically significant bleeding, and demonstrated that most episodes of clinically significant bleeding occur early during admissions to the PICU. These observations suggest patient characteristics and time frames that should prompt vigilant monitoring for clinically significant bleeding.

In terms of preventing clinically significant bleeding, comparative studies of carefully chosen interventions are required. Based on our data, the best candidate for such an intervention is platelet transfusion. Both our retrospective and prospective studies identified thrombocytopenia as a significant risk marker for clinically significant bleeding. Moreover, there is obvious conceptual rationale for attempting platelet transfusion in order to correct thrombocytopenia and possibly ameliorate bleeding risk. An appropriate patient population to study would have to be identified. In other words, a level of thrombocytopenia that might be expected to benefit from platelet transfusion – a transfusion threshold – would need to be determined.

Restricting attention to that minority of patients with a significant degree of thrombocytopenia would likely mean that a study of prophylactic platelet transfusion would have to be conducted across several centres, in order to accrue enough patients. Fortunately, in Canada platelet concentrates are a well-standardized product. Furthermore, platelet counts are a reproducible test. A

multi-centre trial of prophylactic platelet transfusions, then, would seem to be feasible.

This study would be most efficient if it employed a comprehensive definition of clinically significant bleeding, such as the one that we employed in our studies. By using a broadly-inclusive definition of clinically significant bleeding, we were able to demonstrate a higher incidence of clinically significant bleeding, particularly when this definition was applied prospectively, than any previous study. In the context of a randomized trial, this translates into more outcome events, potentially a larger absolute risk reduction with the proposed intervention, and ultimately a smaller intended sample size for the trial.

Another important function of such a study would be to investigate the possible effect of abnormal values of INR, PTT, and fibrinogen concentration on bleeding risk in the setting of significant thrombocytopenia. Because a randomized trial of prophylactic platelet transfusions would require consent from patients or their substitute decision-makers, the study protocol could include systematic collection of these other laboratory parameters, to better examine their importance.

This effort could produce data that would provide more rational use of laboratory investigations and blood products. Most importantly, improved patient care could result.

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Appendices

Appendix 1: Case Report Forms for Retrospective Study

Patient's Initials: _ _ Patient Enrolment Number: _ _ _ _ _

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU CASE REPORT FORM

1. DEMOGRAPHICS

1.1 Date of Birth: |_ _| |_ _| |_ _| |_ _ _ _|
D D M M M Y E A R

1.2 Admission to PICU date/time: |_ _| |_ _| |_ _ _| |2|0|0|9| *at* |_ _|:|_ _|
D D M M M Y E A R H H M M

1.3 Gender: |_| *Male* |_| *Female*

1.4 Weight: |_ _ _|.|_| ***kg***

1.5 Admission Diagnosis: _____

2. EXCLUSION CRITERIA

2.1 Admitted to PICU for bleeding |_| *yes* |_| *no*

If "yes", specify site _____

2.2 Previously diagnosed bleeding disorder |_| *yes* |_| *no*

If "yes", specify _____

2.3 Weight < 5 kg |_| *yes* |_| *no*

2.4 Age < 2 months (60 days) or >= 18 years |_| *yes* |_| *no*

2.5 Prior inclusion during study period |_| *yes* |_| *no*

If "yes", record Enrolment # _____

|_| **Eligible → Complete CRF**

|_| **Excluded** (*if meets any exclusion criteria*) **→ Do not collect other data**

Patient's Initials: |__|__|__| Patient Enrolment Number: |__|__|__|__|__|__|

3. CLINICAL DATA

3.1 Vitals at admission

Heart rate	beats / min
Blood pressure	/ mmHg
Respiratory rate	breaths / min
O_2 Sat	_____% on _____% O_2 _____ L / min
Temperature	_____ ^oC |__| oral |__| rectal |__| axillary |__| bladder

3.2 Nutrition: |__| NPO |__| TPN |__| tube feed, specify device: _____ |__| oral

3.3 Respiratory support: |__| yes, specify type _____ |__| no

3.4 Antibiotics (*started from 24 hours before admission to 6 hours after admission*)

Drug	Dose (specify units)	Route	Frequency (specify units)	Date / Time of 1st Administration D D / M M M /Y E A R	H H : M M
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

3.5 Antacids (*started from 24 hours before admission to 6 hours after admission*)

Drug	Dose (specify units)	Route	Frequency (specify units)	Date / Time of 1st Administration D D / M M M /Y E A R	H H : M M
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

3.6 Steroids (*started from 24 hours before admission to 6 hours after admission*)

Drug	Dose (specify units)	Route	Frequency (specify units)	Date / Time of 1st Administration D D / M M M /Y E A R	H H : M M
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

Patient's Initials: __ __ __ Patient Enrolment Number: __ __ __ __ __

3.7 Anticoagulants *(started from 24 hours before admission to 6 hours after admission)*

Drug	Dose (specify units)	Route	Frequency (specify units)	Date / Time of 1st Administration DD / MMM / YEAR	HH : MM
				__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
				__ __ / __ __ __ / 2 0 0 9	__ __ : __ __

3.8 Procoagulants *(started from 24 hours before admission to 6 hours after admission)*

Drug	Dose (specify units)	Route	Frequency (specify units)	Date / Time of 1st Administration DD / MMM / YEAR	HH : MM
				__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
				__ __ / __ __ __ / 2 0 0 9	__ __ : __ __

3.9 Blood Products *(given from 24 hours before admission to 6 hours after admission)*

Product	Dose (specify units)	Date / Time of Administration DD / MMM / YEAR	HH : MM
		__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
		__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
		__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
		__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
		__ __ / __ __ __ / 2 0 0 9	__ __ : __ __

3.10 Procedures *(performed from 24 hours before admission to 6 hours after admission)*

Procedure	Date / Time of Procedure DD / MMM / YEAR	HH : MM
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __
	__ __ / __ __ __ / 2 0 0 9	__ __ : __ __

Patient's Initials: __|__|__| Patient Enrolment Number: __ __ __ __ __

4. LABORATORY DATA *(Values closest to date & time of admission)*

Test		Result	Date / Time of Test *D D / M M M / Y E A R H H : M M*
Hemoglobin		g / L	|__|__ __ __ __| 2 0 0 9 __ __ : |__ __
Platelet Count	|__| clotted	x 10^9 / L	
PTT	|__| periph |__| art line |__| CVL	s	|__|__ __ __ __| 2 0 0 9 __ : |__ __
Fibrinogen		g / L	
INR			
ALT		U / L	|__|__ __ __ __| 2 0 0 9 __ __ : |__ __
AST		U / L	
Creatinine		µmol / L	|__|__ __ __|__| 2 0 0 9 __ __ : |__ __
Urea		mmol / L	
pH	|__| ABG		|__|__ __ __|__| 2 0 0 9 __ __ : |__ __
pCO_2	|__| CBG	mm Hg	
HCO_3^-	|__| VBG	mmol / L	

5. OUTCOME

\|__\| Episode of clinically significant bleeding → **Complete CRF for bleeding episode**

\|__\| Duration of PICU admission > 7 days

\|__\| Discharge from PICU on \|__\|__\| / \|__\|__\| / \|__\|__\|__\|\|2\|0\|0\|9\| at \|__\|__\| : \|__\|__\|
D D / M M M / Y E A R H H : M M

\|__\| Death on \|__\|__\| / \|__\|__\| / \|__\|__\|__\|\|2\|0\|0\|9\| at \|__\|__\| : \|__\|__\|
D D / M M M / Y E A R H H : M M

Patient's Initials: |__|__|__ Patient Enrolment Number: __|__|__|__|__

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU CASE REPORT FORM – SIGNIFICANT BLEEDING EVENT

1. BLEEDING EVENT

1.1 Date and time of bleeding event: |__|__ __|__ __| |2 0 0|9| at __ __:|__|__
D D / M M / Y E A R H H : M M

1.2 Detection of bleeding event (*specify site*)**:**

|__| Clinical observation: _____

|__| Radiographic observation: _____

1.3 Type of bleeding event (*indicate all that apply*)**:**

1. Blood loss or hematoma formation is thought to have caused any of the following:

|__| Death

|__| Hypotension (*PALS definition*)

|__| Decrease in hemoglobin concentration by at least 20 g / L from baseline

2. Blood loss or hematoma formation caused significant symptoms or impairment of function.

|__| Specify: _____

3. Blood loss or hematoma formation resulted in any of the following interventions:

|__| Cardiopulmonary resuscitation

|__| Surgical management of blood loss (*specify below*)

|__| Major revision or reinforcement of a surgical dressing (*specify below*)

|__ Procedural or operative investigation of blood loss (*specify below*)

__| Use of volume expanders in volumes > 20 mL / kg (*specify below*)

__| Transfusion of PRBC

__| Use of medication or blood products to control bleeding (*specify below*)

|__| Cessation of anticoagulation medication (*specify below*)

|__ Delay or avoidance of an essential or urgent procedure or intervention (*specify below*)

Patient's Initials: |__|__|__| Patient Enrolment Number: |__|__|__|__|__|

2. MANAGEMENT *(in the 6 hours following clinically significant bleeding event)*

2.1 Volume Expanders *(excluding PRBCs – list under Blood Products)*

Volume Expander	Dose / Volume *(specify units)*	Date / Time of Administration *D D / M M M /Y E A R*	*H H M M*
		|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
		|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

2.2 Blood Products

Blood Product	Dose *(specify units)*	Date / Time of Administration *D D / M M M /Y E A R*	*H H M M*
		|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
		|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
		|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

2.3 Medications *(stopped or started – dose/route/frequency and date/time if started)*

Medication	Dose *(units)*	Route	Freq *(units)*	Date / Time of 1st Administration *D D / M M M /Y E A R*	*H H M M*
	or Stopped			|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
	|__| *stopped*				
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
	|__| *stopped*				
				|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|
	|__| *stopped*				

2.4 Procedures & Investigations *(delayed or performed – date/time if performed)*

Procedure or Investigation	Delayed or Performed	Date / Time of Procedure or Investigation *D D / M M M /Y E A R*	*H H M M*
	|__| *delayed* |__| *performed*	|__|__| |__|__|__| |2|0|0|9	|__|__|:|__|__|
	|__| *delayed* |__| *performed*	|__|__| |__|__|__| |2|0|0|9	|__|__|:|__|__|
	|__| *delayed* |__| *performed*	|__|__| |__|__|__| |2|0|0|9|	|__|__|:|__|__|

2.5 Control of Bleeding: \|__\| *yes* \|__\| *no* \|__\| *uncertain*

Appendix 2: Instructions for Case Report Forms for Retrospective Study

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU CASE REPORT FORM – INSTRUCTIONS

General Instructions

- At the top of each page, enter the Patient's Initials (first, last), and the Patient Enrolment Number
- Enter dates in the format DD / MMM / YYYY (i.e. October 22, 1998 is 22 / OCT / 1998)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4 pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A.
- To correct an entry, draw a line through the incorrect response, write and circle your initials, record the date of the correction, and enter the valid information. See example below:

Blood Pressure: 120 / ~~76~~ 93 (RW) 12/Dec/02

1. DEMOGRAPHICS

1.3 Take date and time of PICU admission from nursing admission note. (If time of admission is not available there, may take from other sources, such as PICU flow sheet or physician order sheet.)

1.5 Use weight at time of admission to the PICU, taken from nursing admission note. (If weight is not recorded on nursing admission note, may take from other sources, such as ER documentation, physician order sheet, or PICU flow sheet.)

1.6 Admission diagnosis is to be determined from documentation at admission (nursing note, physician note).

2. EXCLUSION CRITERIA

Determination of whether a patient meets an exclusion criterion is based only on information available *at time of admission.*

A patient may meet more than one exclusion criterion. If a patient meets *any* of the exclusion criteria, mark as "Excluded", and collect no further data.

2.1 A patient meets this criterion if admitted to the PICU specifically for control or

monitoring of bleeding. Intra-operative bleeding does not meet this criterion, unless it is not controlled at the time of admission to PICU. If a patient is admitted to the PICU because of bleeding, specify the site.

2.2 If a patient has a *previously diagnosed* bleeding disorder, specify the disorder.

2.5 If a patient has a prior inclusion during the study period, record the enrolment number of that prior inclusion.

3. CLINICAL DATA

3.1 Use vitals as recorded on nursing admission note. If data are not recorded on nursing admission note, take first recorded value from PICU flow sheet.

If patient is on room air, record as 21 % O_2.

Record site of temperature measurement.

3.2 Record patient's source of nutrition *at time of admission* to PICU. If patient is tube fed, specify device (ex. NG tube, G-tube).

3.3 If a patient is receiving respiratory support *at time of admission to PICU*, record type (ex. CPAP, BiPAP, I + V). If intubated and ventilated, specify type of ventilation (ex. Conventional, HFOV, HFJV). Supplemental oxygen alone, whether given by nasal prongs or facemask, should not be recorded as respiratory support and should be recorded under vitals (**3.1**).

3.4 – 3.9 Record only medications or blood products given during the period from 24 before admission to PICU to 6 hours after admission to PICU. Record date and time of *first administration* during this period. Record medications taken *at home* that are likely to have been taken in the 24 hours prior to admission to PICU, even if administration is not documented, and record date / time as "home med". Do not record medications or blood products given *after* an episode of clinically significant bleeding.

Record *generic drug name*, dose including units, route of administration, and frequency for all drugs. Record "x1" for a one-time dose of a drug, including date and time of the dose. For a drug given as a continuous infusion, record any bolus dose as a one-time dose; record rate of infusion, record frequency as "infusion", and record date and time of beginning of the infusion.

3.4 Do not include topical or inhaled antibiotic drugs.

3.5 Including ranitidine, pantoprazole, omeprazole, lansoprazole, aluminum hydroxide.

3.6 Include corticosteroids only. Do not include topical or inhaled steroid drugs.

3.7 Including warfarin, unfractionated heparin (UFH) given as an infusion or in bolus doses greater than 10 units / kg, low molecular weight heparin (LMWH, Enoxaparin, Dalteparin, Tinzaparin), aspirin (ASA), ibuprofen, ketorolac, indomethacin, celecoxib, tissue plasminogen-activator (tPA, Alteplase).

3.8 Including vitamin K, protamine, tranexamic acid (Cyclokapron), desmopressin (DDAVP, Octostim). Factor concentrates should be recorded under "Blood Products" (3.9).

3.9 Include all blood products, including packed red blood cells (PRBCs), platelets, albumin, immunoglobulin concentrates, factor concentrates (including Octaplex or PCC) and recombinant products. Include blood products used for cardio-pulmonary bypass.

3.10 Include all procedures, even if not successful. Include insertion of central venous lines and arterial lines, but not peripheral intravenous lines. Include surgery, even if this has been recorded under "Admission Diagnosis" (**1.5**). Do not include minor suturing, arterial line removal, central venous line removal, extubation, Foley catheter removal, or other minor procedures.

4. LABORATORY DATA

Record only data obtained during the period from 24 before admission to PICU to 6 hours after admission to PICU. In the case of repeated testing, use results obtained closest to time of admission. Record date and time of test.

For platelet count, if specimen is reported as "clotted", record result, indicate as "clotted".

For PTT, record source of sample.

For blood gasses, indicate if arterial (ABG), capillary (CBG), or venous (VBG). Use test taken closest to the time of admission. In the case that two different blood gases are taken at the same time, use ABG or, if ABG is not available, use CBG.

5. OUTCOME

Record *one and only one* outcome for each patient.

If a patient has an episode of clinically significant bleeding, complete Case Report Form for that episode.

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU
CASE REPORT FORM – SIGNIFICANT BLEEDING EVENT – INSTRUCTIONS

General Instructions

- At the top of each page, enter the Patient's Initials (first, last), and the Patient Enrolment Number
- Enter dates in the format DD / MMM / YYYY (i.e. October 22, 1998 is 22 / OCT / 1998)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4 pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A.
- To correct an entry, draw a line through the incorrect response, write and circle your initials, record the date of the correction, and enter the valid information. See example below:

Blood Pressure: 120 / ~~76~~ 93 (RW) 12/Dec/02

1.1 Record date and time of bleeding event. If time of event is not clearly documented, record time of documentation.

1.2 Record mode of detection of bleeding event (clinical or radiographic) and anatomic site of bleeding. If bleeding event is detected radiographically, record modality (ex. CT, MRI, US,…).

1.3 Record *all* criteria met by bleeding event (more than one may apply).

In order for a criterion to be met, it must be *documented* that the observed blood loss or hematoma formation is thought to have *caused* the observed effect on the patient or to have resulted in an intervention.

1. Hypotension is defined according to Pediatric Advanced Life Support criteria:

   - systolic BP < 70 mm Hg for patients less than 1 year of age
   - systolic BP < 70 + 2 x (age in years) mm Hg for patients between 1 and 10 years
   - systolic BP < 90 mmHg for patients > 10 years of age

   In order to meet the criteria for decreased haemoglobin, haemoglobin concentration must be decreased by at least 20 g / L from the haemoglobin recorded in Section **4** of the patient's Case Report Form.

2. Symptoms or impairment of function may include, but are not limited to:

- signs or symptoms of respiratory distress from hemothorax
- signs or symptoms of cardiovascular dysfunction from hemothorax or hemomediastinum
- signs or symptoms of spinal cord compression from paraspinal hemorrhage
- signs or symptoms of neurologic dysfunction from intracranial hemorrhage
- loss of visual function due to retinal or intraoccular hemorrhage
- pain from hemarthrosis or hematoma formation resulting in loss of function or requiring treatment.

3. Record interventions if they have occurred in response to bleeding.

   Include revision of central line dressings, arterial line dressings, or surgical dressings if the revision was due to bleeding.

   Volume expanders include: albumin 5%, pentastarch, 0.9% normal saline (with or without dextrose or other additives), Ringer's lactate. Use of PRBCs is recorded elsewhere.

   Include use of medications that do not directly affect hemostasis, if the intent of giving the medication is to control bleeding. (ex. H2-blocker or PPI for gastrointestinal bleeding, inhaled or topical epinephrine for epistaxis.)

2 Record management of bleeding if performed or begun *within 6 hours of the bleeding event.*

2.1 Record volume expander used, dose used, and date/time of administration. Albumin 5% should be recorded here. PRBCs should be recorded under Blood Products (2.2).

2.2 Record any blood product used to replace lost blood (PRBCs) or to control bleeding (platelets, cryoprecipitate, FFP, PCC, human-derived or recombinant clotting factor concentrates).

2.3 Record any medications started or stopped to control bleeding. Record date / time of first administration or date / time of stopping.

2.4 Record procedures or investigations performed to control bleeding or to investigate bleeding. Record planned procedures that were delayed because of bleeding.

2.5 In order to record "yes", it must be *documented* that bleeding was stopped or satisfactorily improved, or that the bleeding was no longer evident (ex. for upper GI bleeding, documentation that an NG aspirate was no longer bloody). Similarly, documentation must clearly indicate that bleeding has not been adequately controlled in order to record "no". Otherwise, record "uncertain".

Appendix 3: Case Report Forms for Prospective Study

Patient Enrolment Number: |__|__ __ __| Patient's Initials: __| __ __

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU CASE REPORT FORM

1. DEMOGRAPHICS

1.1 Date of Birth: __|__|__ __|__|__|__
M M M Y Y Y Y

1.2 Admission to PICU date/time: __|__|__|__|__ 2 0 | 1 | 0 | *at* |__|__ :__|__
(= T_{admit}) D D / M M M / Y Y Y Y H H M M

1.3 Gender: __| Male (0) __|Female (1)

1.4 Weight: |__|__|__|.|__| kg

1.5 Admission Diagnosis: _____

|__| Trauma (1)
|__| Post-Op: General (2)
|__| Post-Op: CVT (3)
__| Post-Op: Neuro (4)
__| Post-Op: Ortho (5)
__| Post-Op: Head & Neck (6)
__| Post-Op: Other (7)

__ Medical: Respiratory (8)
__ Medical: Respiratory Infection (9)
__ Medical: Other Infection (10)
__ Medical: Other (11)

1.6 Surgical Patients Only – Estimated Blood Loss: |__|__|__|__|__| mL

2. EXCLUSION CRITERIA

2.1 Admitted to PICU for bleeding __ no __ yes → specify site: _____

2.2 Previously diagnosed bleeding disorder __ no __ yes → specify: _____

2.3 Weight < 3 kg __ no __ yes

2.4 Age < 2 months (60 days) or >= 18 years __ no __ yes

2.5 Prior inclusion during study period __ no __ yes → Enrolment # |__|__, __|__|

2.6 Eligibility

|__| **Eligible → Complete CRF**

|__| **Excluded** (*if meets any exclusion criteria*) → **Do not collect other data**

Patient Enrolment Number: |__|__|__|__| Patient's Initials: |__|__|__|

3. DAY 0: **Start at T_{admit} – 24 hours** = |__|__| |__|__|__| | 2 | 0 | 1 | 0 | *at* |__|__|:|__|__|
End at T_{admit} = |__|__| |__|__|__| | 2 | 0 | 1 | 0 | *at* |__|__|:|__|__|
D D M M M **H H M M**

3.1 Vital Signs:

	Minimum	Maximum
HR (beats / min)		
Systolic BP (mmHg)		
RR (breaths / min)		
O_2 Sat (%)		
Temp (^{o}C)		
	| | PO (1) | | PR (2) | | AX (3) | | BL (4)	| | PO (1) | | PR (2) | | AX (3) | | BL (4)

3.2 Supplemental O_2: |__| no (0) |__| yes (1) → _____ % FiO_2 or _____ L / min

3.3 Intubated: |__| no (0) |__| yes (1)

Resp. Support: |__| conventional (1) |__| CPAP (2) |__| BiPAP (3)
|__| HFOV/HFJV (4) |__| ECMO / bypass (5)

3.4 Enteral Feed: |__| no (0) |__| yes (1) → |__| PO |__| tube feed → device: _____

3.5 Antibiotic: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____
_____/_____

3.6 Steroid: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____

3.7 Antacid: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____

Patient Enrolment Number: |__ __|__ __|__ __| Patient's Initials: |__ __ __|

3.8 Anticoagulant: |__| warfarin (1) |__| heparin (2) |__| LMWH (3)
|__| ASA (4) |__| NSAID (5) |__| tPA (6)
|__| other (7) → specify (drug / route): _____ / _____

3.9 Procoagulant: |__| vit K (1) |__| TXA (2)
|__| DDAVP (3) |__| protamine (4)
|__| other (5) → specify (drug / route): _____ / _____

3.10 Blood Product: |__| PRBC (1) |__| platelets (2)
|__| FFP (3) |__| cryo (4) |__| albumin (5)
|__| immunoglobulin (6) → specify: _____
|__| factor concentrate (7) → specify: _____
|__| cell saver (8)
|__| other (9) → specify: _____

3.11 Procedure: |__| surgery (1) → specify: _____
|__| intubation (2) |__| NG / OG insertion (3) |__| catheter (4)
|__| CVL (5) |__| art line (6) |__| LP (7)
|__| bronchoscopy (8) |__| regional (9) → specify: _____
|__| endoscopy (10) |__| other (11) → specify: _____

3.12 Complete Blood Count Results:

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __
WBC (x 10^9 / L)						
ANC (x 10^9 / L)						
Hemoglobin (g / L)						
Platelets (x 10^9 / L)						

3.13 Coagulation Testing Results

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __
PTT (s)						
Fibrinogen (g / L)						
INR						

Patient Enrolment Number: |__|__ __ '__| Patient's Initials: __ __ __

4. DAY 1: **Start at T_{admit}** = __ __ |__|__ __ | 2 0 | 1 0 *at* |__ __ : __ __
End at T_{admit} + 24 hours = __ __ |__|__|__ | 2 0 | 1 0 *at* |__ __ : __ __
D D M M M **H H M M**

4.1 Vital Signs:

	Minimum	Maximum
HR (beats / min)		
Systolic BP (mmHg)		
RR (breaths / min)		
O_2 Sat (%)		
Temp (°C)		
	PO (1) PR (2) AX (3) BL (4)	PO (1) PR (2) AX (3) BL (4)

4.2 Supplemental O_2: |__| no (0) |__| yes (1) → _____ % FiO_2 or _____ L / min

4.3 Intubated: |__| no (0) |__| yes (1)

Resp. Support: |__| conventional (1) |__| CPAP (2) |__| BiPAP (3)
|__| HFOV/HFJV (4) |__| ECMO / bypass (5)

4.4 Enteral Feed: |__| no (0) |__| yes (1) → __ PO |__| tube feed → device: _____

4.5 Antibiotic: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____
_____/_____

4.6 Steroid: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____

4.7 Antacid: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____

Patient Enrolment Number: __ __ __ __ Patient's Initials: __ __ __

4.8 Anticoagulant: __ warfarin (1) __ heparin (2) __ LMWH (3)
__ ASA (4) __ NSAID (5) __ tPA (6)
__ other (7) → specify (drug / route): _____ / __ __

4.9 Procoagulant: __ vit K (1) __ TXA (2)
__ DDAVP (3) __ protamine (4)
__ other (5) → specify (drug / route): _____ / __

4.10 Blood Product: __ PRBC (1) __ platelets (2)
__ FFP (3) __ cryo (4) __ albumin (5)
__ immunoglobulin (6) → specify: __ _____
__ factor concentrate (7) → specify: __ _____
__ cell saver (8)
__ other (9) → specify: _____

4.11 Procedure: __ surgery (1) → specify: _____
__ intubation (2) __ NG / OG insertion (3) __ catheter (4)
__ CVL (5) __ art line (6) __ LP (7)
__ bronchoscopy (8) __ regional (9) → specify: _____
__ endoscopy (10) __ other (11) → specify: _____ / ____

4.12 Complete Blood Count Results:

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __
WBC (x 10^9 / L)						
ANC (x 10^9 / L)						
Hemoglobin (g / L)						
Platelets (x 10^9 / L)						

4.13 Coagulation Testing Results

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __	__ __ / __ __ *at* __ __ : __ __
PTT (s)						
Fibrinogen (g / L)						
INR						

Patient Enrolment Number: __ __|__|__ Patient's Initials: __ __|__

5. DAY 2: **Start at T_{admit} + 24 hours** = __ __ |__ __ __| 2 0 | 1 | 0 *at* |__ __ : __ __
End at T_{admit} + 48 hours = __ __| __ __ __| 2 0 | 1 0 *at* |__ __ :|__ __|
D D M M M **H H M M**

5.1 Vital Signs:

	Minimum	Maximum
HR (beats / min)		
Systolic BP (mmHg)		
RR (breaths / min)		
O_2 Sat (%)		
Temp (^{O}C)		
	| PO (1) PR (2) AX (3) | BL (4)	| PO (1) | PR (2) AX (3) | BL (4)

5.2 Supplemental O_2: |__| no (0) |__| yes (1) → _____ % FiO_2 or _____ L / min

5.3 Intubated: |__| no (0) |__| yes (1)

Resp. Support: |__| conventional (1) |__| CPAP (2) |__| BiPAP (3)
|__| HFOV/HFJV (4) |__| ECMO / bypass (5)

5.4 Enteral Feed: |__ no (0) __ yes (1) → __ PO |__ tube feed → device: _____

5.5 Antibiotic: |__| no (0) __ yes (1) → specify (drug / route): _____/_____
_____/_____
_____/_____

5.6 Steroid: __| no (0) __ yes (1) → specify (drug / route): _____/_____
_____/_____

5.7 Antacid: __| no (0) __ yes (1) → specify (drug / route): _____/_____
_____/_____

Patient Enrolment Number: __ __ __ Patient's Initials: __ __ __

5.8 Anticoagulant: |__ warfarin (1) |__ heparin (2) |__ LMWH (3)
|__ ASA (4) |__ NSAID (5) |__ tPA (6)
|__ other (7) → specify (drug / route): _____/_____

5.9 Procoagulant: |__ vit K (1) |__ TXA (2)
|__ DDAVP (3) |__ protamine (4)
|__ other (5) → specify (drug / route): _____/_____

5.10 Blood Product: |__ PRBC (1) |__ platelets (2)
|__ FFP (3) |__ cryo (4) |__ albumin (5)
|__ immunoglobulin (6) → specify: _____
|__ factor concentrate (7) → specify: _____
|__ cell saver (8)
|__ other (9) → specify: _____

5.11 Procedure: |__ surgery (1) → specify: _____
|__ intubation (2) |__ NG / OG insertion (3) |__ catheter (4)
|__ CVL (5) |__ art line (6) |__ LP (7)
|__ bronchoscopy (8) |__ regional (9) → specify: _____
|__ endoscopy (10) |__ other (11) → specify: _____

5.12 Complete Blood Count Results:

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__
WBC (x 10^9 / L)						
ANC (x 10^9 / L)						
Hemoglobin (g / L)						
Platelets (x 10^9 / L)						

5.13 Coagulation Testing Results

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__	__/__ *at* __:__
PTT (s)						
Fibrinogen (g / L)						
INR						

Patient Enrolment Number: __|__|__ __ Patient's Initials: __|__|__

6. DAY 3: **Start at T_{admit} + 48 hours** = __ __|__ __ __|2 0 1 0 *at* __ __|:__ __
End at T_{admit} + 72 hours = __ __|__ __ __|2 0 1 0 *at* __ __|:__ __
D D M M M **H H M M**

6.1 Vital Signs:

	Minimum	Maximum
HR (beats / min)		
Systolic BP (mmHg)		
RR (breaths / min)		
O_2 Sat (%)		
Temp (^{O}C)		
	PO (1) PR (2) AX (3) BL (4)	PO (1) PR (2) AX (3) BL (4)

6.2 Supplemental O_2: |__| no (0) |__| yes (1) → _____ % FiO_2 or _____ L / min

6.3 Intubated: |__| no (0) |__| yes (1)

Resp. Support: |__| conventional (1) |__| CPAP (2) |__| BiPAP (3)
|__| HFOV/HFJV (4) |__| ECMO / bypass (5)

6.4 Enteral Feed: __ no (0) |__| yes (1) → __ PO |__| tube feed → device: _____

6.5 Antibiotic: __| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____
_____/_____

6.6 Steroid: |__| no (0) __| yes (1) → specify (drug / route): _____/_____
_____/_____

6.7 Antacid: |__| no (0) |__| yes (1) → specify (drug / route): _____/_____
_____/_____

Patient Enrolment Number: |__|__|__|__| Patient's Initials: |__ __ __

6.8 Anticoagulant: |__| warfarin (1) |__| heparin (2) __ LMWH (3)
|__| ASA (4) |__ NSAID (5) __ tPA (6)
|__| other (7) → specify (drug / route): _____ / _____

6.9 Procoagulant: |__| vit K (1) |__ TXA (2)
|__| DDAVP (3) |__| protamine (4)
|__| other (5) → specify (drug / route): _____ / _____

6.10 Blood Product: |__| PRBC (1) |__| platelets (2)
|__| FFP (3) |__| cryo (4) __ albumin (5)
|__| immunoglobulin (6) → specify: _____
|__| factor concentrate (7) → specify: _____
|__| cell saver (8)
|__| other (9) → specify: _____

6.11 Procedure: |__| surgery (1) → specify: _____
|__| intubation (2) |__| NG / OG insertion (3) __ catheter (4)
|__| CVL (5) |__ art line (6) __| LP (7)
|__| bronchoscopy (8) |__ regional (9) → specify: _____
|__| endoscopy (10) |__ other (11) → specify: _____

6.12 Complete Blood Count Results:

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __
WBC (x 10^9 / L)						
ANC (x 10^9 / L)						
Hemoglobin (g / L)						
Platelets (x 10^9 / L)						

6.13 Coagulation Testing Results

	Date / Time (DD / MMM / 2010 *at* HH:MM)					
	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __	__ / ___ *at* __ : __
PTT (s)						
Fibrinogen (g / L)						
INR						

Patient Enrolment Number: |__|__.__ __. Patient's Initials: |__|__ __

7. OUTCOMES

7.1 Patient Disposition: |__| Duration of PICU admission > 72 hours (1)

|__| Discharge from PICU (2)
→ specify date / time: |__|__|__|__|__|__| | 2 | 0 | 1 | 0 | at |__|__|:|__|__|
D D M M M H H M M

|__| Death in PICU (3)
→ specify date / time: |__|__|__|__|__|__| | 2 | 0 | 1 | 0 | at |__|__|:|__|__|
D D M M M H H M M

7.2 Clinically Significant Bleeding: |__| no (0)
|__| yes (1)→ **Complete CRF for <u>each</u> bleeding episode**

When all CRFs for this admission are complete: Record dates and times of bleeding events in chronological order below. Identify *at most one* event as the Primary Event.

(Primary Event = first episode of clinically significant bleeding that is *not* chest tube bleeding from a post-op cardiovascular surgery patient.)

		Primary Event
Date / Time of 1st event:	|__|__|__|__|__|__|	2	0	1	0	at |__|__|:|__|__|	|__|
Date / Time of 2nd event:	|__|__|__|__|__|__|	2	0	1	0	at |__|__|:|__|__|	|__|
Date / Time of 3rd event:	|__|__|__|__|__|__|	2	0	1	0	at |__|__|:|__|__|	|__|
Date / Time of 4th event:	|__|__|__|__|__|__|	2	0	1	0	at |__|__|:|__|__|	|__|
	D D M M M H H M M	

Patient Enrolment Number: __|__|__.__. Patient's Initials: |__|__|__.

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU
CASE REPORT FORM – SIGNIFICANT BLEEDING EVENT

1. BLEEDING EVENT

1.1 Date and time of bleeding event: |__|__| __ __|__|__| 2 | 0 1 0 | at __ __|: __|__
D D / M M M / Y Y Y Y H H M M

1.2 Detection of bleeding event (*specify site*)**:**

|__| Clinical observation: _____

|__| Radiographic observation: _____

1.3 Post-op cardiac surgery AND chest tube bleeding: |__| yes |__| no

1.4 Type of bleeding event (*indicate all that apply*)**:**

1. Blood loss or hematoma formation is thought to have caused any of the following:

|__| Death

|__| Hypotension (*PALS definition*)

|__| Decrease in hemoglobin concentration by at least 20 g / L from baseline

2. Blood loss or hematoma formation caused significant symptoms or impairment of function.

|__| Specify: _____

3. Blood loss or hematoma formation resulted in any of the following interventions:

__ Cardiopulmonary resuscitation

__ Surgical management of blood loss (*specify below*)

__ Major revision or reinforcement of a surgical dressing (*specify below*)

__ Procedure, radiography, test, or consult to investigate blood loss (*specify below*)

__ Use of volume expanders in volumes > 20 mL / kg or transfusion of PRBC (*specify below*)

__ Use of medication or blood products to control bleeding (*specify below*)

__ Cessation of anticoagulation medication (*specify below*)

__ Delay or avoidance of an essential or urgent procedure or intervention (*specify below*)

Patient Enrolment Number: __-__-__-__| Patient's Initials: |__|__ __.

2. VITAL SIGNS (*measurements closest to, but prior to, clinically significant bleeding event*)

HR: _____ beats min Systolic BP: _____ mmHg RR: _____ breaths min
O_2 Sat: _____ % Temp: _____ ^{O}C |__| PO (1) |__| PR (2) |__| AX (3) |__| BL (4)

3. MANAGEMENT (*in the 6 hours following clinically significant bleeding event*)

3.1 Volume Expanders (*excluding PRBCs & albumin – list under Blood Products*)

Volume Expander	Dose / Volume (*specify units*)	Date / Time of Administration D D / M M M /Y E A R H H : M M

3.2 Blood Products

Blood Product	Dose (*specify units*)	Date / Time of Administration D D / M M M /Y E A R H H : M M

3.3 Medications (*stopped or started – dose/route/frequency and date/time if started*)

Medication	Dose (*units*)	Route	Freq (*units*)	Date / Time of 1st Administration D D / M M M /Y E A R H H : M M
	|__| started |__| stopped			
	|__| started |__| stopped			

3.4 Procedures & Investigations (*delayed or performed – date/time if performed*)

Procedure or Investigation	Delayed or Performed	Date / Time of Procedure or Investigation D D / M M M /Y E A R H H : M M
	|__| delayed |__| performed	
	|__| delayed |__| performed	
	|__| delayed |__| performed	

3.5 Control of Bleeding: |__| yes |__| no |__| uncertain
Comment: _____

Appendix 4: Instructions for Case Report Forms for Prospective Study

DEVELOPING A PREDICTION TOOL FOR CLINICALLY SIGNIFICANT BLEEDING IN THE PICU CASE REPORT FORM – INSTRUCTIONS

General Instructions

- At the top of each page, enter the Patient's Initials (first, last), and the Patient Enrolment Number
- Enter dates in the format DD / MMM / YYYY (i.e. October 22, 1998 is 22 / OCT / 1998)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4 pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A.
- To correct an entry, draw a line through the incorrect response, write and circle your initials, record the date of the correction, and enter the valid information. See example below:

Blood Pressure: 120 / ~~76~~ 93 (RW) 12/Dec/02

1. DEMOGRAPHICS

1.2 Take date and time of PICU admission from nursing admission note. (If time of admission is not available there, may take from other sources, such as PICU flow sheet or physician order sheet.)

1.4 Use weight at time of admission to the PICU, taken from nursing admission note. (If weight is not recorded on nursing admission note, may take from other sources, such as ER documentation, physician order sheet, or PICU flow sheet.)

1.5 Admission diagnosis is to be determined from documentation at admission (nursing note, physician note). Record the *reason for admission to PICU* (ex. aspiration pneumonia), not underlying conditions (ex. cerebral palsy). Patients are considered "post-op" only if admission to PICU was planned following the OR. Patients who are admitted to the PICU because of unexpected perioperative complications should be coded according to those complications.

- trauma = forceful trauma *only*
- medical = all other medical conditions, including burns, drowning, hanging

1.6 For post-op patients only, record estimated blood loss in mL as documented in the OR note. For non-surgical patients, record "N/A".

2. EXCLUSION CRITERIA

Determination of whether a patient meets an exclusion criterion is based only on information available *at time of admission.*

A patient may meet more than one exclusion criterion. If a patient meets *any* of the exclusion criteria, mark as "Excluded", and collect no further data.

2.1 A patient meets this criterion if admitted to the PICU specifically for control or monitoring of bleeding, or of symptoms attributable to bleeding (ex. monitoring for neurologic symptoms or increased intracranial pressure due to intracranial hemorrhage). Intra-operative bleeding does not meet this criterion, unless it is not controlled at the time of admission to PICU. If a patient is admitted to the PICU because of bleeding, specify the site.

2.2 If a patient has a *previously diagnosed* inherited bleeding disorder, specify the disorder.

2.5 If a patient has a prior inclusion during the study period, record the enrolment number of that prior inclusion.

3. DAY 0

Record the date and time of admission (T_{admit}) and the date and time 24 hours prior to admission (T_{admit} – 24 hours). This time period is Day 0.

3.1 Record the maximum and minimum values of all vital signs recorded during Day 0. Record site of temperature measurement (PO = oral, PR = rectal, AX = axilla, BL = bladder).

3.2 If patient received supplemental O_2 at any time during Day 0, mark "yes" and record *maximum* % O_2 or FiO_2 recorded during Day 0.

3.3 If patient is intubated at any time during Day 0, mark "yes". Record all forms of respiratory support received during Day 0. (Mark all that apply.)

- conventional = conventional ventilation
- CPAP = Continuous Positive Airway Pressure, either by mask or ET tube
- BiPAP = Bimodal Positive Airway Pressure, either by mask or ET tube
- HFOV = High Frequency Oscillator Ventilation
- HFJV = High Frequency Jet Ventilation
- ECMO = Extra-Corporeal Membrane Oxygenation

3.4 If patient received any enteral feeding during Day 0, mark "yes" and indicate PO feed or indicate tube feed and specify device. Both PO and tube feed may be marked, if both types of feeding occurred during Day 0.

3.5 – 3.7 If medications were given during Day 0, mark "yes" and indicate *generic drug name* and route of administration.

3.5 Do not include topical or inhaled antibiotic drugs.

3.6 Including ranitidine, pantoprazole, omeprazole, lansoprazole, aluminum hydroxide.

3.7 Include corticosteroids only. Do not include topical or inhaled steroid drugs.

3.8 Record all anticoagulant medications given during Day 0.

- heparin = unfractionated heparin (UFH) given as an infusion or in bolus doses greater than 10 units / kg.
- LMWH = Enoxaparin, Dalteparin, Tinzaparin,...
- ASA = aspirin
- NSAID = ibuprofen, ketorolac, indomethacin, celecoxib,...
- tPA = tissue plasminogen-activator (Alteplase).

3.9 Record all procoagulant medications given during Day 0. Clotting factor concentrates should be recorded under "Blood Products" (3.10).

- vit K = vitamin K
- TXA = tranexamic acid (Cyclokapron)
- DDAVP = desmopressin (Octostim)

3.10 Record all blood products given during Day 0, including blood products used in the OR or for cardiopulmonary bypass or ECMO.

- PRBC = packed red blood cells
- FFP = fresh frozen plasma
- cryo = cryoprecipitate platelets
- immunoglobulin = intravenous immunoglobulin (IVIg), varicella immune globulin (VZIg), anti-D (WinRho), rituximab, ...
- cell saver = cell saver blood

3.10 Record all procedures and attempted procedures attempted or performed during Day 0. Record surgery, even if already recorded under Admission Diagnosis (**1.5**). Do not include peripheral IV insertion, suctioning, minor suturing, arterial line removal, central venous line removal, extubation, Foley catheter removal, or other minor procedures.

- surgery = all surgical procedures, including chest tube insertion
- intubation = endotracheal intubation
- NG = nasogastric tube
- OG = orogastric tube
- catheter = foley catheter or intermittent urinary catheter insertion
- CVL = central venous line insertion at any site (IJ or femoral venous line, PICC line, dialysis catheter,...)
- art line = arterial line at any site
- LP = lumbar puncture for any purpose (diagnostic, intrathecal medication administration, regional anaesthesia,...)
- regional = regional anaesthesia other than LP
- endoscopy = upper or lower GI tract endoscopy

3.11 Record the results of *all* Complete Blood Counts done during Day 0, and the date and time of each test.

3.12 Record the results of *all* coagulation testing done during Day 0, and the date and time of each test.

When data collection for Day 0 is completed, indicate at the bottom of Page 3.

4, 5 & 6 See instructions for Section **3**.

7. OUTCOME

7.1 Record *one and only one* disposition for each patient.

7.2 Indicate whether any episode of clinically significant bleeding (according to the study definition) occurred during Days 1, 2 or 3. Complete a bleeding CRF for each episode of clinically significant bleeding that occurs during that time period. Record the date and time of each clinically significant bleeding event. When the CRF is completed, identify *at most one* event as the patient's primary bleeding event.

DEVELOPING A PREDICTION TOOL FOR
CLINICALLY SIGNIFICANT BLEEDING IN THE PICU
CASE REPORT FORM – SIGNIFICANT BLEEDING EVENT – INSTRUCTIONS

General Instructions

- At the top of each page, enter the Patient's Initials (first, last), and the Patient Enrolment Number
- Enter dates in the format DD / MMM / YYYY (i.e. October 22, 1998 is 22 / OCT / 1998)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4 pm is entered 16:00)
- If data is not applicable, not known, illegible, or incorrect, enter N/A.
- To correct an entry, draw a line through the incorrect response, write and circle your initials, record the date of the correction, and enter the valid information. See example below:

Blood Pressure: 120 / ~~76~~ 93 (RW) 12/Dec/02

1.4 Record date and time of bleeding event. If time of event is not clearly documented, record time of documentation.

1.5 Record mode of detection of bleeding event (clinical or radiographic) and anatomic site of bleeding. If bleeding event is detected radiographically, record modality (ex. CT, MRI, US) and anatomic site of bleeding.

1.6 If the patient's reason for admission is Post-Op Cardiac *and* the bleeding is chest tube output, mark "yes"; otherwise mark "no".

1.7 Record *all* criteria met by bleeding event (more than one may apply).

In order for a criterion to be met, it must be the clear opinion of the bedside physician that the observed blood loss or hematoma formation is thought to have *caused* the observed effect on the patient or to have resulted in an intervention.

1. Hypotension is defined according to Pediatric Advanced Life Support criteria:

   - systolic BP < 70 mm Hg for patients less than 1 year of age
   - systolic BP < 70 + 2 x (age in years) mm Hg for patients between 1 and 10 years
   - systolic BP < 90 mmHg for patients > 10 years of age

   In order to meet the criteria for decreased haemoglobin, haemoglobin concentration must be decreased by at least 20 g / L from the *last haemoglobin recorded prior to the onset of bleeding* (sections **4.12**, **5.12**, or **6.12**) or, in the

case of bleeding whose onset is prior to any measurement of haemoglobin after admission, from the last haemoglobin recorded prior to admission (**3.12**).

2. Symptoms or impairment of function may include, but are not limited to:

   - signs or symptoms of respiratory distress from hemothorax
   - signs or symptoms of cardiovascular dysfunction from hemothorax or hemomediastinum
   - signs or symptoms of spinal cord compression from paraspinal hemorrhage
   - signs or symptoms of neurologic dysfunction from intracranial hemorrhage
   - loss of visual function due to retinal or intraoccular hemorrhage
   - pain from hemarthrosis or hematoma formation resulting in loss of function or requiring treatment.

3. Record interventions if they have occurred in response to bleeding.

   Include revision of central line dressings, arterial line dressings, or surgical dressings if the revision was due to bleeding.

   Volume expanders include: pentastarch, 0.9% normal saline (with or without dextrose or other additives), Ringer's lactate, or albumin 5%.

   Include use of medications that do not directly affect hemostasis, if the intent of giving the medication is to control bleeding. (ex. H2-blocker or PPI for gastrointestinal bleeding, inhaled or topical epinephrine for epistaxis.)

3 Record the last set of vital signs taken prior to the onset of bleeding. Indicate site of temperature measurement.

4 Record management of bleeding if performed or begun *within 6 hours of the bleeding event.*

4.1 Record volume expander used, dose used, and date/time of administration. PRBCs and albumin 5% should be recorded under Blood Products (**3.2**).

4.2 Record any blood product used to replace lost blood (PRBCs) or volume (albumin 5%), or to control bleeding (platelets, cryoprecipitate, FFP, PCC, human-derived or recombinant clotting factor concentrates).

4.3 Record any medications started or stopped to control bleeding. Record date / time of first administration or date / time of stopping.

4.4 Record procedures or investigations (lab tests or radiographic tests) or consultations performed to control bleeding or to investigate bleeding. Record planned procedures or interventions that were delayed because of bleeding.

4.5 Mark "yes" or "no" if, in the opinion of the bedside physician, bleeding was or was not stopped or satisfactorily improved. Otherwise, mark "uncertain".

Appendix 5: Prompt Sheet for Bedside Clinicians for Prospective Study

Developing a Prediction Tool for
Clinically Significant Bleeding in the PICU

Interventions:

- Use of **Volume Expanders** or transfusion of **PRBC**
- Revision or reinforcement of a **Dressing**
- **Medication** or **Blood Products** to control bleeding
- **Procedure** or **Surgery** to investigate or control bleeding
- **Heparin**, **LMWH**, or other anticoagulant medication stopped
- Delay or avoidance of a **Procedure** or **Intervention**
- **CPR** (cardiopulmonary resuscitation)
- **CT**, **MRI** or other **Scan** or **Test** to investigate bleeding
- Change in **Ventilation**

Symptoms:

- New or changed **Respiratory Symptoms**
- **Paralysis**, **Seizures** or other neurologic symptoms
- Loss of **Vision**
- **Pain** resulting in loss of function or requiring treatment

Effects on Patient:

- **Death**
- **Hypotension**
- Decrease in **Hemoglobin** concentration