Predicting Physiologic Responses to Transfusion in Critically Ill Children

Mid-term Project Plan
Team White

Mich Fredericks, Andrew Jin, Gaurav Sharma, Jasen Zhang, Roger Zou
Engineering PI: Dr. Sarma, and Clinical PI: Dr. Bembea

Team Member Contributions

Each member performed the following:

- Read biomedical papers
- Brainstormed problems and approaches to the project
- Attended weekly meetings with Dr. Bembea, Dr. Greenstein, and Dr. Sarma

Listed are members and their specific contributions:

Mich Fredricks (ECE, Undergraduate)

- Calculated statistics about data that indicated to clinical PI that the initial dataset was incomplete
- Extracted subset of patients from dataset who have undergone blood transfusions as well as transfusion times and most recent hemoglobin lab results to transfusions

Andrew Jin (BME, Undergraduate)

- Extracted patient transfusion information
- Powerpoints
- Project proposal revisions

Gaurav Sharma (1st Year, BME, MSE student)

- Edited parts of the proposal
- Extracted PICU stay information from minute-to-minute data
- Liaison between PIs and team

Jasen Zhang (ChemBE, Undergraduate)

- Drafted project aims and approach parts to the proposal.
- Brainstormed questions and problems pertaining to our dataset.
- Collected demographic data of patients

Roger Zou (1st Year, BME, PhD student)

- Drafted “Approach” and “Timeline” portions of the proposal
- Edited proposal
- Edited powerpoint presentations

Project Aims

Anemia affects 74% of critically ill children in the Pediatric Intensive Care Unit (PICU). The transfusion of red blood cells (RBCs) can be a lifesaving procedure to ameliorate severe anemia or shock, which may result in multi-organ failure and death [1]. Approximately 50% of children with a stay of ≥2 days in the North American PICUs receive at least one RBC transfusion [1]. The primary goal of an RBC transfusion is to increase the hemoglobin (Hb) concentration to reverse dangerous declines in oxygen delivery and oxygen consumption [2,3]. Inadequate oxygen delivery results in tissue hypoxia and subsequently irreversible tissue death. However, inappropriate exposure to RBCs can increase the risk of adverse events, including infections and noninfectious serious hazards of transfusion (NISHOTs) such as transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), or transfusion-related immunomodulation (TRIM) [4]. In the pediatric population, adverse effects are over twice as prevalent compared to the general population [5].

Currently, physicians in the PICU rely heavily on Hb concentration to make transfusion decisions. The current consensus among physicians is that clinical judgment, including the consideration of patient history, physical exam, current status, among countless other variables, must be factored in the decision making process. This leads to the high variability in transfusion decisions beyond a simple Hb threshold, and also makes it difficult to predict patient responses. While physiologic understanding of some goals expected from transfusion response and physiologic recommendations for transfusion has been outlined (**Figure 1**), it has not been implemented or well understood [1,5]. That is, there is no clear relationship determined between RBC transfusion and clinically relevant outcomes, due to the lack of relevant cause-effect relationships between RBC transfusions, physiologic metrics (including those related to anemia intolerance) and clinically significant outcomes [1].

Recommendations to improve the decision-making process for transfusion in the PICU can only be made after such relationships are established. Thus, the ultimate goal of this project is to develop a quantitative method to guide the decision-making process for transfusion in the PICU that will maximize responsiveness and minimize adverse outcomes. Specifically, we will develop a computational framework using generalized linear models (GLMs) that utilizes electronic medical record data from 2,155 consecutive patients admitted to the PICU at the Johns Hopkins Hospital from July 2014 to October 2015 to predict (i) physiologic responses to transfusions and (ii) adverse outcomes from transfusions. There are a total of 865 transfusion events in this data set, and 372 of these patients have received at least one transfusion. The data set aggregates a comprehensive record of admissions, laboratory measurements, vital signs, medications, and procedures from the electronic medical record, along with bedside minute-to-minute physiologic data. We will develop our computational framework through the following aims:

Aim 1: Apply statistical tests to identify key physiological features that significantly differ between pre- and post-transfusion states in children admitted to the PICU.

We will use statistical tests such as paired T-tests and Wilcoxon rank-sum tests to evaluate which physiologic metrics and biomarkers related to oxygen delivery and consumption recorded in the electronic health record (EHR) and minute-to-minute (M2M) data, including lactate and heart rate, change the most, i.e are most discriminative from pre- to post-transfusion. Variables that are relevant to the consensus physiologic understanding of anemia will be investigated first, followed by the interrogation of all available variables. *We hypothesize that statistical tests will reveal specific variables, such as lactate and heart rate, that significantly differ from pre- to post-transfusion.*

Aim 2: Apply generalized linear models (GLMs) to predict select post-transfusion physiologic measurements from pre-transfusion physiologic measurements.

The algorithm will take as input all physiologic measurements tabulated in the EHR, to predict selected post-transfusion physiologic measurements of interest, including heart rate, blood pressure, and various measurements of oxygen delivery. *We hypothesize that the GLM approach will robustly predict these post-transfusion physiologic measurements that will inform physicians on the quantitative physiological effects of their intervention.*

Variables	Normal Values	Suggested Threshold[a]	References: Pediatrics	References: General
Physiologic metric				
Heart rate	Age dependent	120–130% of baseline?		(78, 79)
Blood pressure	Age dependent	70–80% of baseline?		(80)
Respiratory rate/dyspnea	Age dependent	120–130% of baseline?		
Capillary refill time (s)	≤ 2	> 3?	(80)	
Core–peripheral temperature Δ		TBD		
Sto_2 (near-infrared spectroscopy)		TBD		(81–90)
Dynamic Sto_2	TBD	TBD		(91)
O_2 delivery (mL/O_2/kg/min)	11.0–14.0	7.0?	(92)	(93, 94)
O_2 consumption (mL/O_2/kg/min)	3.0–3.5	< 3.0 or 80–90% of baseline?	(95–97)	(98)
Central vein oximetry (%)	65–75%	~ 50–60%?	(99, 100)	(101–103)
Systemic O_2 extraction	20–30%	40–50%?	(92)	
Peripheral O_2 extraction	TBD	TBD		(104)
Heart rate variability	TBD in children	TBD		(105–107)
Plethysmographic variability index	TBD	TBD		(108)
Functional capillary density	TBD	TBD		
Biomarkers				
Lactate (mmol/L)	< 1.5	> 3.0	(109–112)	(113)
Gastric tonometry (gastric intramucosal pH, pHi)	pHi > 7.35 or $\Delta Paco_2$–$Ptoco_2$ < 5 mm Hg	pHi ≤ 7.35 or $\Delta Paco_2$–$Ptoco_2$ ≥ 5 mm Hg?	(114)	(115, 116)
Cytochrome oxidase redox	TBD	TBD		(117)

pHi = intramucosal gastric pH, $Ptoco_2$ = Pco_2 measured by gastric tonometry, Sto_2 = tissular O_2 saturation, as measured by near-infrared spectroscopy, TBD = to be determined.
Delta (Δ) represents change, difference, or gradient.
[a]The clinical usefulness of almost all thresholds listed in this table remains TBD. Furthermore, it must be underlined that change over time could even more informative than a given value: for example, a change (Δ) in lactate level from 7 to 4 mmol/L tells us that the patient is improving, whereas a lactate level of 4 mmol/L suggests that the health status of the patient is alarming if the data are interpreted alone.

Figure 1: Examples of Physiologic Metrics and Biomarkers Reporting Loss of Reserve in Compensating for Oxygen Delivery Insufficiency or Reporting Failure of Oxygen Delivery Homeostasis [3]

Aim 3: Apply GLMs to predict the likelihood of adverse effects through pediatric multi-organ dysfunction syndrome (MODS) upon giving transfusion from pre-transfusion physiologic measurements.

The algorithm will take as input pre-transfusion physiologic measurements tabulated in the EHR, to predict the likelihood of developing an adverse event to post-transfusion. *We hypothesize that the GLM approach will robustly predict the likelihood of adverse outcomes given the patient's pre-transfusion physiologic measurements, which will further inform physicians on the likelihood that their intervention will be effective and minimize adverse outcomes (specifically new and progressive MODS).*

Significance

About 74% of critically ill children in PICU who stay more than 2 days have been observed to have anemia [6]. In critically ill children with hemorrhagic shock or with severe anemia, RBC transfusions can be lifesaving. The aim of transfusion is to increase Hb concentration to improve overall oxygen delivery. However, over-prescription of transfusions also greatly increases the risk of adverse events, including infections and noninfectious serious hazards of transfusion (NISHOTs) [4,7,8,9,10]. Thus, every transfusion decision needs to balance the benefit of increased oxygen delivery and the risks of morbidity and mortality associated with its adverse effects.

Currently, physicians rely heavily on Hb concentration to make transfusion decisions. Indeed, it has been demonstrated that administering RBC transfusion improves clinical outcomes if the pre-transfusion Hb is less than 5 g/dL [11]. However, administering transfusions at 7 g/dL is no worse than a more liberal cutoff of 9.5 g/dL in the stabilized pediatric critically ill patient [12]. Thus between these 5 g/dL and 7 g/dL thresholds, clinical judgment must be used, resulting in large variability in the decision making process that is both patient and physician specific. In addition, it is not currently known what an appropriate Hb threshold is for patients who are not hemodynamically stable, who are hypoxic, or who have specific disorders (e.g., congenital heart disease, traumatic brain injury, etc). Data-driven insights that can help the physician in transfusion decision making in these gray areas and will be beneficial to improving patient outcomes.

Innovation

A predictive tool that provides information at the bedside on both the expected changes in physiologic parameters (e.g. heart rate, blood pressure, and markers of oxygenation delivery and consumption) and the likelihood of adverse outcomes, has not been implemented. This is especially true in the PICU, where patients are unstable, physiologic responses are not well characterized, and decisions must be made quickly. Given the ambiguity associated with decision to transfuse between 5g/dL and 7g/dL in the stabilized PICU patient, and unknown thresholds for transfusion in the unstable PICU patient and patients with specific disorders (e.g., congenital heart disease, traumatic brain injury), such a tool would be extremely valuable to physicians at the bedside.

Leveraging generalized linear modeling for transfusion outcome predictions as a clinical tool in the PICU is also novel. While physiologic responses to transfusion has been well studied in the context of both clinical trials and animal models (although not in the PICU population), predictive models that estimate transfusion outcomes given pre-transfusion physiologic measurements have not been developed. Finally, prediction of the likelihood of adverse events given the patient's state pre-transfusion will be a useful clinical tool to help physicians weigh the risks versus benefits of their intervention.

Approach

Description of Data

The study population will consist of an already collected dataset which includes 2,155 pediatric patients, admitted to the Johns Hopkins Hospital PICU from July 2014 to October 2015. We will only include patients of younger than 18 years of age in our study. 372 patients have received at least one transfusion. In total, 865 transfusions were administered. The racial, gender, and age distributions in our data set are summarized in Tables 1, 2 and 3.

Table 1: Summary of age distribution of the PICU subjects

Age at first PICU Admit	No. of Subjects	Percentage of dataset
0-2	729	33.8%
3-8	545	25.3%
9-12	293	13.6%
13-18	512	23.8%
19+*	76	3.5%

*Excluded from study population

Table 2: Summary of racial distribution of subjects

Race	No. of Subjects	Percentage
White	959	44.5%
African Am.	763	35.4%
All Other Races	261	20.1%

Table 3: Summary of gender distribution of subjects

Gender	No. of Subjects	Percentage
Male	1190	55.2%
Female	961	44.6%
Unknown	4	0.2%

Procedural Overview

First, we will perform exploratory data analysis by obtaining summary statistics for variables pertaining to patient demographics (e.g. gender, age, race, etc) and those with physiologic relevance to the medical understanding of physiologic response to transfusions (e.g. blood pressure, respiratory rate, etc). The full list of relevant variables can be found in Fig. 5. We will initially assume the log of all biomarkers that are not percentages (e.g. SpO_2) have a normal distribution.

Then, we will build a generalized linear model to predict select physiologic parameters after transfusion using pre-transfusion physiological measurements recorded in the EHR. Finally, we will build a generalized linear model to predict the probability of a transfusion being associated with a future adverse event (specifically, with development of new and progressive MODS). Further validation will allow the models to become useful clinical tools that help clinicians understand the predicted outcome of transfusions for the specific presenting patient at the bedside.

Figure 5. Physiologic Variables to be investigated

Heart rate/heart rate variability (M2M variable)
SpO2 (M2M variable)
PaO2*
Oxygenation Index (OI) **
Oxygenation Saturation Index**
Arterial BP (SBP, DBP, MAP)
ScvO2
NIRS/rSO2
CVP***
Lactate
Capillary refill time
Core Temperatures****
Peripheral Temperatures*****

* Only available in patients with an arterial catheter in place
** Only for mechanically ventilated patients AND with an arterial catheter in place
*** Only available in patients with a central venous catheter in place
**** Recorded as rectal, esophageal, bladder, or blood
***** Recorded as toe, axillary, skin, or ear

Training and Testing Data Set

We will split the data into demographically equivalent training and testing sets before we start working on any of the aims. The testing data will neither be used to identify features that discriminate pre- and post-transfusion patient state nor will it be used to build GLMs. The testing dataset will be exclusively used to test the final models.

Identify Cohort of PICU Patients

Patients have a heterogeneous course through the hospital. For example, patients are admitted to the hospital, PICU, and various other locations, often many times during their stay. Transfusions may also be administered many times during a single stay. Furthermore, the data itself is currently divided among many multiple files and formats. Thus, we will first computationally generate a merged dataset that aggregates all data for each patient into one table. We will also narrow the window of study to the first PICU or hospital admission to standardize the cohort. Patients also move between hospital beds for procedures or imaging studies, and this leads to multiple seemingly different PICU admissions in the database. Thus, if the difference between two PICU admissions is less than 24 hours, it is considered as one PICU admission. Transfusion performed over subsequent hours is considered a single transfusion event. Cohort 1 will include the index admission of all

PICU patients <18 years of age during the study period, and all transfusion events during the index PICU admissions. Cohort 2 will be a subset of cohort 1, and will only include the index transfusion event during the index PICU admission, if more than one transfusion was administered during the PICU stay.

Aim 1: Apply statistical tests to identify key physiological features that significantly differ between pre- and post-transfusion states in children admitted to the PICU.

Once we obtain a merged data set for all patients, we will determine which variables in EHRs change significantly after a transfusion. First, we will characterize the distributions of values for each physiologic variable. For example, if the distribution of values for a variable is approximately normal, then we will apply paired sample T-tests to determine for each variable to see if there is a significant difference ($p < 0.05$) between pre- and post-transfusion measurements. Other possible methods include Wilcoxon rank-sum tests for variables that do not follow a normal distribution. We will initially only consider data obtained within 12 hours before or after the blood transfusion to make the comparisons. For physiologic metrics available in the minute-to-minute data, we will evaluate the rate of change pre-, during-, and post-transfusion.

Aim 2: Apply generalized Linear Models (GLMs) to predict select post-transfusion physiologic measurements from pre-transfusion physiologic measurements.

After we study the effects of blood transfusion on key physiologic and laboratory parameters, we will build a model to predict the changes to selected physiologic parameters such as heart rate, blood pressure, and measures of blood oxygenation (e.g. SpO_2, PaO_2, oxygenation saturation index, etc) after blood transfusions. We will construct GLMs to predict the expected value of each outcome variable post-transfusion, given the entire set of variables recorded in the EHR and M2M data before transfusion. For example, consider the heart rate variable. Taking the log of heart rate transforms the variable space to real numbers, and thus log(heart rate) can be modeled with a normal distribution $y_{HR} \sim N(\mu_{HR}, \sigma_{HR})$, where y_{HR} is the random variable representing log(heart rate) and is normally distributed with mean μ_{HR} and standard deviation σ_{HR}. Then we have a linear regression model such that:

$$y_{HR} = \beta_0 + \sum_{i=1}^{N} \beta_i x_i^{pre} \quad (1)$$

where N is the number of input EHR and M2M variables before transfusion, β_i are linear parameters and x_i^{pre} are the input features pre-transfusion. Solving for the β (using maximum likelihood estimation) will yield the complete model for the heart rate response variable. The x_i^{pre} variables are obtained as summary statistics (mean) for the w hours immediately before transfusion, where w is clinically determined for each input feature. The same scheme applies for other post-transfusion variables such as SpO_2 and blood pressure; inherent to the model design, each outcome variable will be independently predicted. GLMs have a distinct advantage in this case because we cannot assume each variable is gaussian. The set of patients will be randomly into demographically equivalent training and testing sets; k-fold cross-validation on the training set will be performed, with mean squared error as a measure of accuracy. Independent accuracy measurement using the test set will also be performed.

K-fold cross-validation involves splitting the training set into a given k number of different equally sized sections and creating k different models trained excluding one of the sections. The withheld section for each model is then used as a validation set and the accuracy (mean squared error) of the k models are averaged. By considering both the averaged accuracies from cross-validation and the real accuracy from the traditionally split training and testing dataset accuracy, we will make better decisions on whether this model accurately predicts post-transfusion physiologic variables.

The output of our model will be a collection of predicted vital signs post transfusion that have been determined as being relevant by clinicians in classifying the success of a transfusion. These variables include but are not limited to heart rate, arterial blood pressure, lactate levels, peripheral capillary oxygen saturation, and partial pressure of oxygen. Because of the multivariate nature of our output, our model will most likely be a combination of multiple models, one to predict each output feature.

Aim 3: Apply GLMs to predict the likelihood of adverse effects through pediatric multi-organ dysfunction syndrome (MODS) upon giving transfusion from pre-transfusion physiologic measurements.

We will next use GLMs to predict the probability of new and progressive MODS in patients who received a transfusion. MODS occurs in our dataset with unknown frequency at this time. The likelihood of patients developing MODS post-transfusion is defined as π, which will be modeled to depend on a set of N explanatory variables $x_i, .., x_N$. Thus the canonical link function is as follows:

$$log(\tfrac{\pi}{1-\pi}) = \gamma_0 + \sum_{i=1}^{N} \gamma_i x_i^{pre} \quad (2)$$

where N is again the number of input variables available from EHR. Representing the model in this way allows for solving each γ using maximum likelihood estimation. Similar to Aim 2, the data set will be split into test and training sets, and k-fold cross-validation will be performed on the training sets. For each iteration of cross validation, the k-1 folds will compute a value of γ which can be implemented on the 1 validation fold to predict likelihoods of developing new and progressive MODS. A receiver operator characteristic (ROC) curve will be used to quantify how well γ distinguished between patients who will or will not develop MODS. A θ^* will be extracted from each ROC curve which maximizes prediction accuracy.

The completion of k-fold cross-validation will result in k γ values, k ROC curves, and k θ^* thresholds. We will evaluate the stability of γ and θ^* values among the k folds and determine whether they are stable enough to be used on the testing set. Ultimately, we will apply the optimal γ and θ^* values taken from the entire training set and implement them on the testing set to obtain final specificity, sensitivity, and accuracy values of our prediction model.

Milestones & Timeline

Week of 9/10
- First meeting with Dr Bembea on Thursday, 9/13
- Learned about the complications of blood transfusions and the need for further studies

Week of 9/17
- Read papers giving insight into current transfusion practices

Week of 9/24
- Meeting with Dr Sarma on Wednesday, 9/26
- Brainstormed project problems and goals
- Second meeting with Bembea on Thursday, 9/27 with an introduction to the data
- Obtained pre-processed EHR Data for each subject from Mr Granite

Week of 10/1
- Clarified confusing points in the dataset
- Preliminary checks of overall patient statistics (documents)

- Third meeting with Dr Bembea on Thursday, 10/4, and clarified which parts of the dataset are most important to consider

Week of 10/8

- Currently gathering more dataset-wide statistics on transfusion, length of PICU admission, age, weight, gender, and race.
- Drafted proposal and presentation

Bi-week of 10/15

- Obtain cleaned and aggregated data for all patients
- Perform summary statistics on clean data
- Finalize proposal and presentation for Wednesday, 10/17 presentation.

Bi-week of 10/29

- Perform statistical tests to evaluate for significant differences in physiologic parameters of our choosing, 12 hours pre- and post-transfusion

Bi-week of 11/12

- Computationally determine the best parameters that maximize the statistical power of differences pre and post transfusion

Bi-week of 11/26

- Brainstorm design of predictive model for patient responses to blood transfusion

Timeline		September		October		November		December	
	Project Preparation								**End of Semester Project Presentation**
0.1	Literature Review to identify difficulties in assessment for pediatric transfusions								
0.2	Identify key patient information that is associated with transfusions								
0.3	Write Project Proposal								
AIM 1	**Identify physiologic differences in pre- and post- transfusion states**								
1.1	Identify and Extract Clean Cohort of PICU Patients								
1.2	Perform Exploratory Data Analysis of PICU Database and determine quantifiable change in vital signs								
1.3	Use statistical analysis methods: paired T-tests, Wilcoxon rank-sum tests, and histograms of M2M and EMR data								
AIM 2	**Apply GLMs to predict post-transfusion physiologic variables from pre-transfusion physiologic variables**								
2.1	Design GLM boilerplate code								

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