An Innovative Framework to Improve Efficiency of Interhospital Transfer of Children in Respiratory Failure

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Abstract

Rationale: High mortality and resource use burden are associated with hospitalization of critically ill children transferred from level II pediatric intensive care units (PICUs) to level I PICUs for escalated care. Guidelines urge transfer of the most severely ill children to level I PICUs without specification of either the criteria or the best timing of transfer to achieve good outcomes.

Objectives: To identify factors associated with transfer, develop a modeling framework that uses those factors to determine thresholds to guide transfer decisions, and test these thresholds against actual patient transfer data to determine if delay in transfer could be reduced.

Methods: A multistep approach was adopted, with initial identification of factors associated with transfer status using data from a prior case-control study conducted with children with respiratory failure admitted to six level II PICUs between January 1, 1997, and December 31, 2007. To identify when to transfer a patient,

thresholds for transfer were created using generalized estimating equations and discrete event simulation. The transfer policies were then tested against actual transfer data.

Measurements and Main Results: Multivariate logistic regression revealed that the absolute difference of a patient's pediatric logistic organ dysfunction score from the admission value, high-frequency oscillatory ventilation use, antibiotic use, and blood transfusions were all significantly associated with transfer status. The resulting threshold policies led to average transfer delay reduction ranging from 0.5 to 2.3 days in the testing dataset.

Conclusions: Current transfer guidelines are devoid of criteria to identify critically ill children who might benefit from transfer and when the best time to transfer might be. In this study, we used innovative methods to create thresholds of transfer that might reduce delay in transfer.

Keywords: children; computer simulation; critical illness; intensive care units; patient transfer

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Pediatric intensive care units (PICUs) are areas within hospitals dedicated to the coordination of care for critically ill and injured children. In the United States,

PICUs have been categorized into level I PICUs, which provide care to the most severely critically ill and injured children, and level II PICUs, where care of the stable

and less severely ill children is coordinated. While published guidelines (1) urge transfer of the most severely ill children from level II to level I PICUs, no objective criteria

exist to aid identification of children who might benefit from transfer and those who might not. This is a formidable challenge faced by physicians in level II PICUs: deciding if and when to transfer patients to level I PICUs.

The need for improved understanding of interhospital transfer decision making and process is underscored by prior reports among critically ill adults (2–7) and children (8–10) that revealed significant adverse outcomes after interhospital transfer to specialized intensive care units (ICUs) in comparison with direct admission to the same units. Also, the timing of transfer is crucial, as increase in duration of illness before interhospital transfer to adult regional ICUs is significantly correlated with higher mortality (11, 12).

Respiratory failure is a leading diagnosis among children transferred from level II to level I PICUs, and it is associated with significant morbidity and mortality within this population of transferred children (10). The objective of the present study was to develop an innovative and systematic framework to enhance decision making that ensures timely transfer of children with respiratory failure from level II to level I PICUs.

Methods

Study Design

The data used for this study were previously collected in the context of a frequency-matched case-control study to investigate the factors associated with transfer (cases) and nontransfer (controls) of children from level II to level I PICUs (13). The two studies had different goals. The original study aimed to better characterize which patients were transferred or not transferred. In the present study, the goal was to come up with a way to prospectively identify thresholds for transfer from which opportunities for reduction in transfer delay could be investigated. Different methodologies were used, and the only overlap was that, after multivariate regression analysis, the derived independent predictors of transfer or nontransfer from the original study were similar to those resulting from the first analytic step in the present study. Thereafter, no similarities existed.

Briefly, the original study involved collection of demographic and physiological

data on children with respiratory failure admitted to six level II PICUs in Michigan and Ohio (13). The study researchers sought to identify factors that might differentiate transferred from nontransferred children. Respiratory failure was defined as the need for positive pressure ventilation. The study was approved by the institutional review boards at the University of Michigan Medical School and at all six participating level II PICU hospitals.

Study Variables

The following variables were included in the study:

1. Patient age
2. Use of specific therapeutic modalities and medical devices while in the PICU (yes/no). (These included high-frequency oscillatory ventilation [HFOV], central venous catheters, arterial catheters, antibiotics, inhaled nitric oxide, steroids, surfactant, and blood transfusion.)
3. Diagnosis of sepsis (yes/no). (Sepsis and respiratory failure are the leading diagnoses associated with level II to I PICU transfer, with associated significant morbidity and mortality [10].)
4. Pediatric logistic organ dysfunction (PELOD) score. (Multiple values of the score were calculated daily, with higher values indicating worse organ dysfunction [14]. The absolute change in PELOD score from each patient's initial baseline score was calculated.)
5. Minimum and maximum heart rate during the level II PICU stay
6. Minimum and maximum systolic blood pressure during the level II PICU stay
7. Length of level II PICU stay
8. Transfer status (A value of 1 corresponded to transfer, 0 to nontransfer.)

A total of 646 patients were included in the study (184 transferred, 462 nontransferred), with 5,397 daily data entries, dependent on the length of stay within the level II PICU. The median patient length of stay was 6 days (range, 0–131 d). The data in this study were evenly split into training and testing datasets.

Initially, each patient's probability of transfer was estimated using binary logistic regression (BLR). Thereafter, a systematic approach was developed to determine when each patient should be transferred, based on the patient's probability of requiring

transfer at each point in time. The decision protocols were validated using discrete event simulation.

Assessment of the Probability of Transfer

As a first step, the training data were used to retrospectively determine which patients had been transferred to a level I PICU. It was assumed that transfer decisions made by the level II PICU physicians were the correct decisions; that is, patients who were transferred were indeed in need of transfer. The goal of the analysis was to design a decision support framework that would enhance identification of patients who would need transfer to level I PICU care.

To predict the need for transfer from level II to level I PICU care, regression analysis was used to model the likelihood of transfer. The regression function incorporated the independent variables specified earlier, including patient age; use of therapeutic modalities; and continuous physiologic parameters such as heart rate, blood pressure, and the rate of change of the PELOD score from one day to the next.

Statistical Analysis

Generalized estimating equations (GEEs) were used to account for within-patient correlation of data points. Briefly, GEE analysis clusters data by patient and considers the effect of a single patient having multiple data points by accounting for the nonindependence of these sequential data points (15). Within GEE, BLR was applied. BLR is a method commonly used to predict the outcome of a dichotomous (yes/no) response variable on the basis of values of continuous and categorical input parameters. Using the training dataset, multivariate regression analysis was used to identify which characteristics played a significant and independent role in predicting transfer. The outcome variable was whether a patient was transferred or not. Backward stepwise BLR with a significance level of 0.05 was used to eliminate insignificant factors when creating the final regression model. The parameter coefficients for each parameter were calculated using least squares estimation.

Identification of When to Transfer a Patient

Next, a framework was developed to determine when each patient would need to be transferred, given each patient's

Figure 1. Flowchart of simulation used to compare transfer policies. PICU = pediatric intensive care unit.

probability of transfer. Policies considered were those under which patients with a probability of transfer greater than a given threshold would be sent to a level I PICU. A discrete event simulation model was applied to the training dataset to select the threshold that would best balance a type I error (transferring a patient who did not need transfer) and a type II error (not transferring a patient who needed transfer).

The algorithm used in the discrete event simulation (16) is depicted in Figure 1. Patient data were updated on a daily basis. After each update, the GEE regression calculated the patient's probability of transfer and compared it with a given threshold. If the probability of transfer exceeded the threshold, a patient was transferred to a level I PICU. Otherwise, the patient remained in the level II PICU. Simulation was censored when the patient left the level II PICU (i.e., no patient data remaining in Figure 1).

The algorithm tested all threshold values between 0 and 1, incrementing by 0.01 units in each iteration. For each iteration, the performance of the algorithm (in terms of patients transferred according to the threshold policy) was compared with actual patient transfers as documented in the dataset. The overall performance of the algorithm was measured by the weighted average of type I error and type II error (Equation 1). In other words, the trade-off between incorrectly transferring a patient versus failing to transfer a patient who needed to be transferred was evaluated depending on weights assigned to both types of error. The simulation calculated which transfer threshold minimized the weighted average of the two errors.

Mathematically, the performance of the policy was given by

$$\text{Performance} = \lambda * \text{Type I Error} + (1 - \lambda) * \text{Type II Error} \quad (1)$$

for $0 \leq \lambda \leq 1$. A value of λ closer to 0 means that it is more important that all patients who need to be transferred are transferred. In particular, $\lambda = 0$ means that only type II error is important. In contrast, a value of λ closer to 1 means that it is more important not to transfer patients who did not need to be transferred; that is, $\lambda = 1$ means that only type I error is important.

Testing of the Threshold Policies

The next step was to test the aforementioned decision-making tool prospectively on the independent testing dataset. The simulation algorithm was run on the testing dataset, and the BLR equation obtained from the training data was used to calculate the probability of transfer. The threshold values from the training set were applied to the testing data, and the error rates in their performance were compared. Statistical analyses were conducted using R version 3.1.2 software (<http://www.r-project.org/>). All simulations were performed in MATLAB version 2013a software (The MathWorks

Table 1. Patient characteristics and use of therapeutic modalities

Characteristic	Training Data	Testing Data	P Value
Mean age, mo (SD)	53.0 (66.2)	42.5 (64.5)	0.08
Central venous catheter, n (%)	140.0 (38)	134.0 (36)	0.61
HFOV, n (%)	19.0 (5)	18.0 (5)	0.85
Nitric oxide, n (%)	8.0 (2)	5.0 (1)	0.40
Surfactant, n (%)	9.0 (2)	7.0 (2)	0.61
Antibiotics, n (%)	328.0 (88)	325.0 (87)	0.60
Steroids, n (%)	175.0 (47)	148.0 (40)	0.04
Blood transfusion, n (%)	118.0 (32)	113.0 (30)	0.66
Sepsis, n (%)	13.0 (4)	6.0 (2)	0.13
Mean PICU stay, d (SD)	9.5 (11.7)	9.5 (15.8)	0.92
Mean maximum change from initial PELOD score (SD)	11.0 (8.7)	10.2 (7.9)	0.15
Mean minimum heart rate, beats/min (SD)	110.7 (26.3)	112.7 (25.6)	0.28
Mean maximum heart rate, beats/min (SD)	153.4 (27.0)	155.5 (26.8)	0.28
Mean minimum systolic blood pressure, mm Hg (SD)	87.9 (18.7)	86.0 (17.6)	0.16
Mean maximum systolic blood pressure, mm Hg (SD)	119.5 (22.2)	117.8 (21.0)	0.28

Definition of abbreviations: HFOV = high-frequency oscillatory ventilation; PELOD = pediatric logistic organ dysfunction; PICU = pediatric intensive care unit.

Table 2. Results of univariate regression analysis

Covariate	Coefficient	Standard Error	P Value
Days in PICU, 10 ⁴	49.410	16.67	<0.01
Age, d, 10 ⁴	−0.820	0.578	0.16
Absolute change from initial PELOD score, 10 ⁴	0.871	0.385	0.02
Minimum heart rate, 10 ⁴	−0.481	0.322	0.14
Maximum heart rate, 10 ⁴	−0.443	0.272	0.10
Minimum systolic blood pressure, 10 ⁴	−1.070	0.462	0.02
Maximum systolic blood pressure, 10 ⁴	−0.205	0.321	0.52
Arterial catheter	0.136	0.258	0.60
Central venous catheter	0.413	0.234	0.08
HFOV	1.567	0.491	<0.01
Nitric oxide	1.444	0.740	0.05
Surfactant	1.278	0.683	0.06
Antibiotics	−0.944	0.327	<0.01
Steroids	−0.429	0.233	0.07
Blood transfusion	0.587	0.240	0.01

Definition of abbreviations: HFOV = high-frequency oscillatory ventilation; PELOD = pediatric logistic organ dysfunction; PICU = pediatric intensive care unit.

For computational purposes, a conversion factor (10⁴) was used in estimating some of the coefficients in the regression analysis.

Inc., Natick, MA). An α of 0.05 was set as the threshold for statistical significance.

Results

Comparisons between the training and testing data revealed no statistically significant differences, except for steroid use (Table 1). In univariate regression analysis, duration of stay in the level II PICU, absolute change from initial PELOD score, minimum systolic blood pressure, use of antibiotics, HFOV, and blood transfusion were significantly associated with transfer status (Table 2). In multivariate regression analysis, the absolute difference of a patient's PELOD score from the initial PELOD score recorded upon admission, whether a patient was on HFOV, required antibiotics, or had blood transfusions were all significantly associated with transfer status (Table 3).

The best threshold values (leading to the smallest weighted sum of errors) are shown in Figure 2. As expected, the optimal threshold depended on the relative importance between type I error and type II error. If a type II error is more important than a type I error, then the optimal threshold is 0, so that the policy transfers all patients as soon as possible. As the importance of type I error increases, the optimal threshold increases, resulting in fewer patients being transferred.

Using the thresholds depicted in Figure 2, comparisons of the timing of transfer were made for all patients in our dataset. As shown in Figure 3, for each patient we calculated the probability that the patient would eventually require to be transferred each day, using our multivariate regression (see Table 3). For instance, suppose a clinician places equal importance on type I error and type II error. In Figure 2, we show that such assessment

would correspond to a threshold of 0.2, so that as long as the patient has a probability of transfer below 0.2, our model suggests not transferring the given patient. In our example, patient (a) (who in reality was never transferred) in Figure 3 started with a probability of transfer of 0.19015 on the day of admission to the hospital. As that probability was below 0.2, our model would have suggested not to transfer the patient, but to wait to get additional patient information. On Days 1, 2, 3, and 4, additional readings were obtained from the patient; yet, none of the readings affected the probability of transfer. On Day 5, however, note that the patient started getting better, which is represented by the slight decrease in the probability of transfer (to 0.19 and later to 0.1899). Using our algorithm, patient (a) would not have been transferred (which closely resembles the decision made by the referring hospitals not to transfer that patient).

However, patient (b) in Figure 3 had a probability of transfer of 0.3159 on Day 0, which increased to 0.316 on Day 2 and to 0.3165 on Day 7. Such a patient would have been transferred on Day 0 (day of admission to the level II PICU) according to our model (as that was the first instance in which the probability of transfer exceeded the threshold of 0.2); yet, the patient was not transferred from the referring hospital until Day 11.

Additionally, we made an assessment of the average transfer delay reduction as a function of relative importance between type I error and type II error after removing outliers. Early transfers greater than 10 days were considered outliers because transfer delay reductions greater than 10 days (from 20 to 40 d) were large and rare and would have led to overestimation of reduction in transfer delay. The threshold policies led to average transfer delay reduction of 0.5–2.3 days in the testing dataset (Figure 4).

Table 3. Results of multivariate regression analysis

Characteristic	β -Coefficient	Standard Error	P Value
Intercept	−0.209	0.307	0.50
Absolute change from initial PELOD score, 10 ⁴	0.961	0.319	<0.01
HFOV	1.33	0.534	0.01
Antibiotics	−1.24	0.349	<0.01
Blood transfusion	0.676	0.287	0.02

Definition of abbreviations: HFOV = high-frequency oscillatory ventilation; PELOD = pediatric logistic organ dysfunction.

For computational purposes, a conversion factor (10⁴) was used in estimating some of the coefficients in the regression analysis.

Discussion

Critically ill children who undergo interhospital transfer from level II PICUs for escalation of care at level I PICUs are at high risk of significant mortality, morbidity, and accompanying high resource use burden at the receiving hospital (10). Among these children, respiratory failure and sepsis accrue the highest mortality

Figure 2. Optimal transfer thresholds are displayed against relative importance between type I error and type II error. The x axis represents the weight given to type I error as a ratio of the weight given to type II error ($\lambda/[1 - \lambda]$) from Equation 1). When the ratio is low (between 0 and 0.6), a type II error is more important than a type I error and the optimal threshold is 0. As the ratio increases, a type II error becomes less important and hence the optimal threshold also increases.

risk and greatest resource use burden (10). The most severely ill children upon arrival at the level I PICU experienced the highest use of invasive technology, such as extracorporeal membrane oxygenation and continuous renal replacement therapy, and had the highest mortality and the most prolonged hospitalization (10). While the decision to transfer a critically ill child from level II PICU care to level I PICU care is likely not straightforward and subject to a host of clinical and nonclinical factors, the stakes are high, given that mortality within level I PICUs is highest among children admitted from level II PICUs (8, 9). If transfer is deemed necessary, physicians need to act quickly to minimize the time until definitive or advanced care is provided, and thus to reduce the patient's

risk for progressive organ dysfunction or death. The simulation findings in the present study suggest that using a GEE regression-based policy can result in earlier transfer decisions, thereby providing patients with level I PICU care sooner than actual transfer practice data would suggest.

Greater likelihood of transfer was predicted by progression of illness severity during the level II PICU stay. Reflected by the absolute change from baseline PELOD score, such disease progression is likely to be associated with a need for escalation of intensive care with requisite organ system support. While organ dysfunction has previously been associated with mortality (14, 17, 18), progressive worsening of organ dysfunction has not hitherto been associated with transfer.

Figure 3. Application of the model to two sample patients: (left panel) a patient who was never transferred to a level I pediatric intensive care unit, and (right panel) a patient who was eventually transferred to a level I pediatric intensive care unit. For each patient, the probability of transfer is recalculated each day as new observations for that patient are obtained. Our model would suggest transferring each patient if the patient's probability of transfer exceeds the optimal threshold that balances type I error and type II error.

Further evidence for clinical deterioration as a trigger for transfer was signaled by the association of blood transfusion and HFOV with heightened likelihood of transfer. Conversely, antibiotic use appeared to be associated with reduced likelihood of transfer, likely indicating response to ongoing intensive care therapy.

Although the present study highlights the importance of progressive organ dysfunction and the need for escalation of organ system support as potential triggers for transfer, it is not clear how to personalize guidelines for transferring patients between PICUs. The aim of the present study was to fill this gap. In particular, using patient-specific data collected from level II PICUs in Michigan and Ohio, systematic assessment of factors associated with transfer status was performed with creation of a data-driven decision framework for how those factors may be used to guide transfer decisions. In this study, we used innovative methods to create thresholds of transfer that might reduce the delay in transfer by 0.5–2.3 days. Such reduction in the delay of transfer has the potential to enhance patient outcomes and reduce resource use burden by permitting early initiation of advanced therapeutic modalities at the level I PICU with the goal of mitigating progression of organ dysfunction.

Similar to recent published work (19), this study highlights the use of innovative healthcare engineering and operations management methods to address complex issues surrounding patient throughput and efficiency of care processes. The interdisciplinary approach involving physician researchers and industrial and operations engineers is unique in its context, though the methods can be replicated by researchers with adequate expertise in other settings. Methods similar to those applied in this study have been used in other clinical settings, including development of optimization models to determine the optimal time to initiate therapy for HIV that maximized the expected lifetime or quality-adjusted lifetime of the patient (20). Another example is the work by Lavieri and coworkers that involved the use of filtering techniques to obtain insights into when to initiate radiation therapy for patients with cancer, based on their prostate-specific antigen dynamics (21). Moreover, while previous research has evaluated how changes in bed

Figure 4. Average reduction in transfer delay is depicted using the optimal transfer thresholds. The x axis represents the weight given to type I error as a ratio of the weight given to type II error ($\lambda/[1 - \lambda]$ from Equation 1). When the ratio is low (between 0 and 0.6), a type II error is more important than a type I error, the optimal threshold is 0, and the policy transfers all patients as soon as possible. As a result, a higher (average) transfer delay reduction (around 2 days for the testing data set) is observed. As the ratio increases, a type II error becomes less important and the average transfer delay reduction also decreases.

assignment might impact ICU occupancy levels and patient wait times (19), the present study is an early foray into the use of these innovative research methods to study the timing of interhospital transfer of critically ill children on the basis of clinical factors. Needless to say, these methods, though not definitive, have the potential to enhance delivery of care to critically ill patients.

The study findings should be interpreted with an understanding of the limitations. Too much emphasis on either type I or type II error would result in

impractical policies of transferring either no patients or every patient, respectively. Hence, it is important to consider both types of error and ensure the best balance possible when deciding which patients should be transferred. The proposed algorithm is meant as a decision support framework and does not include all quantitative and qualitative variables that may impact the need for transfer or transfer decision making. The framework is an innovative initial step to enhance identification of patients in need of transfer, but not a tool that can necessarily supplant clinicians'

decision making and clinical judgment at the bedside. Therefore, it is likely that real-time decision making might lead to transfer even if the probability of needing transfer were below the determined threshold. Analysis of data collected only during hospitalization within the level II PICU setting prevented assessment of the accuracy of actual physician decisions and discrete event simulation of decisions made after transfer or discharge.

Conclusions

Significant mortality and morbidity have been reported among critically ill children with respiratory failure whose care involved transfer from level II to level I PICUs. Current guidelines for transfer are devoid of criteria to identify children who might benefit from transfer and when the best time to transfer might be. In this study, we used innovative methods to create thresholds of transfer that might reduce the delay in transfer by 0.5–2.3 days. Such reduction in the delay of transfer has the potential to enhance patient outcomes and reduce resource use burden by permitting early initiation of advanced therapeutic modalities, thereby mitigating progression of organ dysfunction. Future research is warranted to determine post-transfer outcomes and correlate transfer timing with patient outcomes and resource use. ■

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