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Factors Associated with Inter-hospital Transfer of Children in Respiratory Failure from Level II to Level I Pediatric Intensive Care Units

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Abstract

Purpose—Of all sources of admission to Level I Pediatric Intensive Care Units (PICUs), interhospital transfer admissions from Level II PICUs carry the highest mortality and resource use burden. We sought to investigate factors associated with transfer of children with respiratory failure from Level II to Level I PICUs.

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FO participated in study conception and design, data acquisition and interpretation, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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JGG participated in study conception and design, interpretation of the data, and critical revision of the manuscript.

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Methods—A case-control study was conducted among children with respiratory failure admitted to six Level II PICUs between January 1, 1997, and December 31, 2007, with frequency-matching of 466 non-transferred children (controls) to 187 transferred children (cases).

Results—Among 653 children, transferred children were younger and had more comorbidities. After multivariable analysis, transferred children were more likely to have comorbidities (Odds Ratio [OR]: 2.02; 95% Confidence Interval [CI]: 1.36 – 2.98) and receive escalated care including high frequency ventilation (OR: 2.57; 95%: 1.04 – 6.37) and surfactant therapy (OR 5.33; 95% CI: 1.35 – 21.0).

Conclusions—The study identified patient-level and process-of-care factors associated with transfer from Level II to Level I PICUs. These findings highlight the influence of escalated care on transfer decision-making for critically ill children in respiratory failure.

Keywords

Patient transfer; children; respiratory insufficiency; critical illness; therapeutics

Introduction

Provision of optimal and timely care to critically ill and injured children is essential to ensuring the best possible clinical outcome. Survival for the most severely ill and injured children might be enhanced by admission to highly specialized Level I Pediatric Intensive Care Units (PICU) [1]. Published guidelines advocate for integration of regional systems of PICU services, with transfer of children with high risk of mortality from Level II to Level I PICUs [2]. They urge Level II PICUs to admit children with stable and non-complex disorders and transfer less stable, seriously ill and injured children to Level I PICUs for greater access to advanced technological expertise and subspecialty care capability. The guidelines do not, however, outline criteria to be used by Level II PICUs to identify which patients to transfer to Level I PICUs.

In prior studies, significantly higher unadjusted mortality rates at a Level I PICU were observed among children transferred from Level II PICUs compared with those who were admitted directly from other settings including the emergency department (ED), operating room, or clinics [3,4]. Importantly, however, severity-adjusted mortality was similar across these various sources of admission to the Level I PICU, highlighting the significant influence of pre-transfer illness severity on outcomes at the receiving Level I PICU, and the important need to investigate the determinants of transfer from Level II to Level I PICUs.

The current study was conducted to determine the factors associated with the transfer of children from Level II to Level I PICUs with emphasis on patients in respiratory failure, a leading cause of mortality and morbidity among children transferred to Level I PICU care [5]. It was hypothesized that transfer from Level II PICUs to Level I PICUs would be associated with younger patient age and greater illness severity at initial presentation to the ED of the referring hospital.

Material and Methods

Study Design

A frequency-matched case-control study of children admitted with respiratory failure to six Level II PICUs in Michigan and Ohio, in the Midwest census region of the U.S.

Delineation of PICU Levels of Care

Definition of the Levels of PICU care was in line with prior published guidelines [2]. The level I PICU had to provide multidisciplinary definitive care for a wide range of complex, progressive, and rapidly changing medical, surgical, and traumatic disorders occurring in pediatric patients of all ages, excluding premature newborns. While level I PICUs had to have a full complement of medical and surgical subspecialists, a level II PICU was not required to have the full spectrum of subspecialists. Further, for the purpose of this study, the Level II PICUs did not have the capacity to provide extracorporeal membrane oxygenation for children in respiratory failure.

Setting and Study Population

Definition of Cases and Controls—A case was defined as a patient with respiratory failure who was transferred from one of the six Level II PICUs to one of three Level I PICUs in Michigan, between January 1, 1997, and December 31, 2007. These Level II PICUs were selected given previous referrals to the Level I PICUs. Patients at the same Level II PICU hospitals with the same diagnosis during the same time period, who were not transferred to Level I PICU care, were eligible to be controls.

Exclusion criteria: Medical records of all subjects were reviewed to exclude the following patients due to their inability to be “at risk” for transfer to Level I PICU care:

- Patients who died within 4 hours of Level II PICU admission.
- Patients discharged to the wards within 6 hours of Level II PICU admission.
- Terminally ill patients discharged for “comfort or terminal care” on the ward or at home.

The study was approved by the institutional review boards (IRB) at the University of Michigan Medical School, and at all six participating Level II PICU hospitals.

Selection and Validation of Cases and Controls—A 2-step approach was employed to select and validate the cases and controls.

Step 1: Identification of potentially eligible subjects

At each Level II PICU, admission and discharge log books were queried to identify patients with respiratory failure admitted to the PICU during the study period. These log books were the only source of data with the discharge destination for all patients admitted to the PICUs. Included were all patients in the PICU whose diagnoses included respiratory failure, pneumonia, bronchiolitis, acute respiratory distress syndrome, acute lung injury, or airway obstruction.

Step 2: Identification and validation of cases and controls

All patients with a diagnosis of respiratory failure were identified as potential subjects. Cases were patients transferred from Level II PICU to Level I PICU care while controls were patients not transferred. Controls were frequency matched to the case distribution on diagnosis (respiratory failure) and calendar month (± 3 months of the index case) of PICU admission; from that pool, two or more control subjects were randomly selected per case.

Validation of diagnosis—Each subject's medical record chart was reviewed by the lead investigator (FO) to validate the log book diagnosis of respiratory failure. A diagnosis of respiratory failure was verified by documentation of the use of artificial ventilation (non-invasive or invasive positive pressure ventilation) during the Level II PICU admission.

Validation of non-diagnosis—All transferred patients who did not have a diagnosis of respiratory failure had their medical record reviewed to ensure there was no mis-labeling with a diagnosis that was not respiratory failure. Furthermore, review of the medical records of a random sample (5%) of all non-transferred patients without a diagnosis of respiratory failure was done to ensure that potential control subjects were similarly not erroneously omitted.

In this process, there were no instances of missed cases or controls.

Data collection

For each subject, paper and/or electronic medical records at the Level II PICU hospitals were reviewed in order to abstract the following information, using a standardized data collection form:

1. Demographics: Age and gender.
2. Type of insurance coverage.
3. Pediatric Risk of hospital Admission (PRISA) II score, calculated from data on severity of illness in the ED among children admitted via the ED, with higher values indicating greater illness severity [6].
4. Source of admission to the Level II PICU including the wards, emergency department, or operating rooms of the Level II PICU hospital; or from similar settings at referring hospitals.
5. Use of therapeutic modalities and medical devices (Yes/No) prior to Level II PICU admission. These included antibiotics, vasoactive agents, prostaglandins, steroids, central venous catheters, arterial catheters, tracheal intubation, invasive ventilation, non-invasive ventilation, occurrence and volume of fluid resuscitation (bolus administration of crystalloids and colloids), and the occurrence and volume of blood transfusion.
6. Pediatric Risk of Mortality (PRISM) III score, calculated from data on severity of illness within the first 24 hours of PICU admission, with higher values indicating greater illness severity [7].

7. Use of specific therapeutic modalities and medical devices while in the PICU (Yes/No). These included tracheal intubation, invasive mechanical ventilation (conventional mechanical ventilation & high-frequency ventilation), non-invasive ventilation, renal replacement therapy, central venous catheters, arterial catheters, antibiotics, vasoactive agents, prostaglandins, steroids, fluid resuscitation, and blood transfusion.
8. Pediatric Logistic Organ Dysfunction (PELOD) score: Multiple values of the score were calculated daily, with higher values indicating worse organ dysfunction.⁸ The highest patient-specific daily value was designated the peak PELOD score. Furthermore, at the end of the Level II PICU stay, the proportion of children with organ-specific dysfunction was determined using the PELOD algorithm [8].
9. Comorbidities: Given that comorbid illness was felt to be a potential factor in decision-making regarding transfer or non-transfer to Level I PICU care, patient comorbidities at Level II PICU admission were identified using ICD-9-CM diagnosis codes as enumerated in previous work by Feudtner et al [9]. These diagnoses were ascertained via a thorough search through all secondary diagnosis fields in the medical record charts and included diagnoses in nine separate categories including neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic/immunological, metabolic, other congenital/genetic defect, and malignancy (9). Comorbidities were analyzed as a dichotomous variable (yes/no).

Statistical Analysis

After descriptive analysis, bivariate comparisons of cases and controls in terms of their clinical and demographic characteristics were performed using Chi-square tests for categorical data and the Student t-test or Mann-Whitney U test for continuous data. Specifically, bivariate analyses were conducted to evaluate any differences between cases and controls in: source of PICU admission, comorbidities, PRISA II score (if admitted to the PICU via the ED), type of insurance coverage, age, gender, PRISM III score, peak PELOD score, use of medications (steroids, antibiotics, prostaglandins, vasoactive agents, and surfactant), invasive medical devices (central venous catheters, arterial catheters, tracheal intubation, invasive mechanical ventilation, and renal replacement therapy), non-invasive ventilation, fluid resuscitation, and blood transfusion. Variables that differed between cases and controls, with a p value of < 0.2, were included as potential confounders in subsequent multivariable analysis.

Population-averaged generalized estimating equation (GEE) logistic regression models were fit to estimate the strength of the association (adjusted odds ratio with accompanying 95% confidence interval) between each significant clinical characteristic and transfer status, after controlling for potential confounders. Using the *xtlogit* command in Stata, robust adjustment was made for clustering of data by Level II PICU hospital. The GEE method produces efficient estimators of regression parameters, yields reasonably accurate standard errors, and confidence intervals with the correct coverage rates (10). Interaction effects were not considered. Statistical analyses were conducted using Stata 12 for windows (Stata

Corporation; College Station, Texas, USA), with a two-tailed α level of 0.05 as the threshold for statistical significance.

Results

Data were collected on 653 children with respiratory failure hospitalized at one of six Level II PICUs, 187 of whom were cases and 466 were controls. To ease clarity of presentation of the study findings, cases and controls will henceforth be referred to as transferred and non-transferred patients, respectively.

Pre-PICU clinical course

More than two-thirds (71%) of admissions to the Level II PICUs were from within that hospital (ED 48%, wards 20%, operating room 2%, other settings 1%) while 29% were interhospital transfer admissions from referring hospitals (ED 23%, wards 4%, operating room 1%, other settings 1%). Five percent of the admissions to the Level II PICU had no verifiable source of admission. There was no statistically significant association between source of admission to the Level II PICU and subsequent transfer status ($p = 0.22$). Various therapeutic modalities were deployed prior to Level II PICU admission, including antibiotics (31%), fluid resuscitation (25%), steroids (10%), invasive mechanical ventilation (7%), vasoactive agents (3%), blood transfusion (2%), central venous catheterization (0.6%), non-invasive ventilation (1%), prostaglandin infusion (0.5%), and arterial catheterization (0.3%).

Patient Clinical and Demographic Characteristics

The patient age range was 1 day to 23 years. Overall, transferred children were younger and had more comorbidities than non-transferred children (Table 1). Among the 299 admissions to the Level II PICUs via the ED, there was no statistically significant difference in the ED severity of illness between transferred and non-transferred children assessed using the PRISA II score (20.0 ± 12.4 vs. 18.9 ± 12.2 ; $p = 0.18$). Among all patients, after admission to the Level II PICU, there was no statistically significant difference in illness severity within the first 24 hours of admission as assessed by the PRISM III score, neither was there difference in the peak organ dysfunction as assessed by the PELOD score (Table 1). At the end of the Level II PICU stay, however, a higher proportion of transferred children had multiple organ dysfunction, compared with non-transferred (78% vs. 32%; $p < .001$) children (Table 2).

Use of therapeutic modalities and invasive medical devices in the PICU

Overall, the use of medical devices and therapeutic modalities varied significantly according to transfer status, with transferred children being more likely to undergo central venous catheterization, high frequency ventilation, inhaled nitric oxide therapy, blood transfusion, and administration of vasoactive agents, prostaglandins, and surfactant (Table 3).

Factors associated with transfer status at the end of the Level II PICU stay

After multivariable analysis, depicted in Table 4, transferred children were more likely to have comorbidities (Odds Ratio [OR]: 2.02; 95% Confidence Interval [CI]: 1.36 – 2.98) and receive escalated care including high frequency ventilation (OR: 2.57; 95%: 1.04 – 6.37),

and surfactant therapy (OR 5.33; 95% CI: 1.35 – 21.0). Antibiotic use, steroid therapy and non-invasive ventilation were more likely among children not transferred (Table 4).

Discussion

This study revealed important factors associated with transfer of critically ill children with respiratory failure from Level II PICUs to Level I PICUs in the United States. Transferred children were more likely to have comorbidities, and to receive escalated intensive care including high frequency oscillatory ventilation and surfactant therapy. Response to therapy within the Level II PICU appeared to be associated with low likelihood of transfer as evidenced by children not transferred being more likely to receive antibiotics, steroids, and non-invasive ventilation. In support of the a priori hypotheses, transferred children were younger; however there was no difference in illness severity upon admission regardless of the source of admission. This latter finding might indicate disease progression during the hospitalization as a marker of the need for transfer rather than physiologic status at admission. This assertion warrants further research.

While prior studies of critical care delivery systems have reported variation in outcomes according to the sources of admission to specialized intensive care facilities among adults [11-13] and children [4], they did not investigate the potential role of pre-transfer patient-level and process of care variables such as patient illness severity, response or non-response to intensive care, and the use of various therapeutic modalities within the referring hospitals. The current study extends this area of research by investigating the pre-transfer course of hospitalization to elucidate factors associated with transfer of critically ill children from Level II to Level I PICUs. Although the exact reasons for the highlighted differences by transfer status are unknown, clinically meaningful and biologically plausible explanations can be proffered.

Childhood comorbid illness has been associated with medical fragility, as evidenced by high risk of unscheduled hospitalizations into critical care settings when compared with previously healthy children [14], greater need for rescue by a medical emergency team when hospitalized [15], and the observation that a large proportion of hospitalized children who require cardiopulmonary resuscitation have comorbid illness [16]. The presence of comorbid illness might accentuate physiological vulnerability and heighten the need for transfer to specialized intensive care within a Level I PICU.

The peak PELOD score was assessed as a marker of illness severity during what might be assumed the peak of illness severity. There was no significant difference between the transferred and non-transferred children in the peak PELOD score. The reason for a lack of difference in measured illness severity between the transferred and non-transferred children is unclear but might be related to other multiple variables that inform transfer being more instrumental to the transfer decision-making, or the inability of current illness severity measures to accurately discriminate children who will be transferred from those who would not. This is an assertion that deserves more investigation. Also, given that transferred children were more likely to have multiple organ dysfunction, it might be that multiplicity of

organ dysfunction is a marker and driver of inter-PICU transfer for advanced critical care services at a Level I PICU, rather than measured illness severity, as utilized in the study.

High frequency oscillatory ventilation (HFOV) is often deployed as rescue therapy among critically ill children with severe hypoxemic respiratory failure that is unresponsive to conventional modes of ventilator therapy [17, 18]. In a prior single center study of children transferred from Level II to Level I PICU care, 25% of them required extracorporeal membrane oxygenation therapy, an invasive therapy reserved for failure of conventional and non-conventional ventilator therapy for hypoxemic respiratory failure [5]. It was therefore instructive to observe more transferred children undergoing HFOV compared with children who were not transferred, since failure to respond would likely trigger transfer to Level I PICU care.

Surfactant therapy has been investigated as an adjunctive therapy to enhance lung compliance and oxygenation in pediatric respiratory failure, by reducing alveolar surface tension. Although surfactant replacement therapy has been beneficial in preterm neonates with respiratory distress syndrome, clinical trials to date have not revealed any efficacy of surfactant therapy in pediatric respiratory failure [19]. Given this lack of evidence for its efficacy, the association of surfactant use with transfer to Level I PICUs might reflect a “last-ditch” effort to improve pulmonary function in children with severe hypoxemic respiratory failure unresponsive to therapy, prior to transfer.

It could be surmised that inter-hospital transfer might be a marker for poor response or non-response to ongoing clinical therapy, with resultant poor outcomes, as previously reported among ward-to-ICU transfers [20]. The converse might also hold true: that response to therapeutic modalities might be reflected in physiological improvement, leading to lower likelihood of transfer. This theoretical construct might underpin the study finding that antibiotic therapy, steroid therapy, and non-invasive ventilation were associated with lower likelihood of transfer. While the pathophysiologic pathways to explain this finding are likely not straightforward, it likely is a proxy signal for overall clinical improvement negating the need for inter-hospital transfer, rather than signify a causal relationship. These findings are novel and hypothesis-generating, and future research is warranted to elucidate patient-level determinants of response or non-response to intensive care therapy.

The study findings should be interpreted in light of certain limitations. For example, unobserved factors such as bed availability at the Level I PICU might play a role in the transfer medical decision-making. The authors applied rigorous methods to identify the cases and controls in the study. However, given the heterogeneity in the causes of respiratory failure in the study cohort, the specific etiology of each child’s respiratory failure could not be readily delineated. Nonetheless, all patients were deemed in respiratory failure given their need for positive pressure ventilation. Comparability between cases and controls can be a concern in case-control studies. Therefore, in the design and conduct of the study, rigorous systematic methods were employed to choose cases and controls using comparable selection criteria and significantly reduce the likelihood of misclassification of diagnostic criteria. Although the study was regional in scope, the findings could be applicable to the

forty U.S. States where there is a combination of Level I and II PICUs and inter-hospital transfer of critically ill children is likely to occur [21].

In conclusion, the study identified patient-level and process-of-care factors associated with transfer or non-transfer of critically ill children from Level II to Level I PICU care. These findings have significant potential to enhance future iterations of guidelines for inter-PICU transfer, and could be used as a foundation for future development of clinical prediction rules to guide optimal transfer of critically ill children with respiratory failure.

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Abbreviations

PICU	Pediatric intensive care unit
PRISM	Pediatric Risk of Mortality
ED	Emergency Department
PRISA	Pediatric Risk of hospital Admission
PELOD	Pediatric Logistic Organ Dysfunction
HFOV	High Frequency Oscillatory Ventilation

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Table 1

Clinical and Demographic Characteristics by Transfer Status

Characteristic	Overall (n = 653)	Transferred (n = 187)	Non-Transferred (n = 466)	p
Male Gender (%)	56.1	55.1	56.5	0.70
Age in Years				
Mean (SD)	4.4 (5.8)	3.3 (5.4)	4.4 (5.9)	0.03
Median (IQR)	1 (0-8)	1 (0-5)	2 (0.8)	0.004
PRISM III-24 Score				
Mean (SD)	7.3 (6.7)	7.4 (6.5)	7.2 (6.8)	0.72
Median (IQR)	6 (3-11)	6 (3-11)	6 (2-10)	0.58
Comorbidities (%)	55.3	66.8	50.4	0.001
Peak PELOD Score				
Mean (SD)	14.2 (9.5)	13.7 (10.3)	14.4 (9.2)	0.38
Median (IQR)	11 (10-20)	11(10-21)	11 (11-20)	0.15
Payer Type (%)				
Private	54.2	50.8	55.6	0.14
Medicaid	40.2	42.1	39.5	
Self-Pay	3.2	3.3	3.1	
Uninsured	0.5	0	0.7	
Other	1.9	3.8	1.1	

SD = Standard Deviation, IQR = Inter-quartile range, PRISM = Pediatric Risk of Mortality, PELOD = Pediatric Logistic Organ Dysfunction ..

Table 2

Organ Dysfunction at the end of Level II PICU Stay by Transfer Status

Characteristic (%)	Overall (n = 653)	Transferred (n = 187)	Non-Transferred (n = 466)	p
Any Organ Dysfunction	45.2	77.9	32.2	< 0.001
Neurologic Dysfunction	13.5	19.9	10.9	0.001
Cardiac Dysfunction	27.4	41.9	21.7	< 0.001
Renal Dysfunction	2.3	5.4	1.1	0.001
Hematological Dysfunction	1.4	3.2	0.6	0.011
Hepatic Dysfunction	3.7	8.6	1.7	< 0.001

PICU = Pediatric Intensive Care Unit.

Table 3

Use of Medical Devices and Therapeutic Modalities by Transfer Status

Characteristics (%)	Overall (n = 653)	Transferred (n = 187)	Not Transferred (n = 466)	p
Arterial Catheters	24.4	25.1	24.0	0.77
CVC	36.9	45.5	33.5	0.004
Non-Invasive Ventilation	37.1	18.7	44.4	< 0.001
HFOV	5.4	10.2	3.4	0.001
Inhaled Nitric Oxide	2.0	3.7	1.3	0.042
RRT	0.15	0.2	0	0.526
Vasoactive agents	24.2	31.0	21.5	0.01
Prostaglandins	2.0	7.0	0	< 0.001
Antibiotics	85.9	78.1	89.1	< 0.001
Steroids	45.0	36.4	48.5	0.005
Fluid Resuscitation	59.6	56.2	60.9	0.259
Blood Transfusion	28.9	35.8	26.2	0.014
Surfactant	2.3	4.8	1.3	0.007

CVC = Central Venous Catheter, RRT = Renal Replacement therapy, HFOV = High Frequency Oscillatory Ventilation.

Table 4

Logistic Regression Model of Level II to Level I Pediatric Intensive Unit Transfer

Characteristics	Adjusted Odds Ratio (95% CI)
Comorbidity	1.92 (1.38 – 2.69)
High Frequency Oscillatory Ventilation	2.57 (1.04 – 6.37)
Non-Invasive Ventilation	0.31 (0.20 – 0.48)
Surfactant Therapy	5.33 (1.35 – 21.0)
Antibiotic therapy	0.36 (0.21 – 0.61)
Steroid Use	0.65 (0.44 – 0.97)

The adjusted odds ratio reflects the odds of the specified outcome compared to the reference category within the same variable; adjusted for patient age, insurance coverage, gender, central venous catheterization, inhaled nitric oxide therapy, vasopressor use, blood transfusion, and peak Pediatric Logistic Organ Dysfunction score.