Characteristics of Medically Transported Critically Ill Children with Respiratory Failure in Latin America: Implications for Outcomes

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Abstract

Several challenges exist for referral and transport of critically ill children in resource-limited regions such as Latin America; however, little is known about factors associated with clinical outcomes. Thus, we aimed to describe the characteristics of critically ill children in Latin America transferred to pediatric intensive care units for acute respiratory failure to identify risk factors for mortality. We analyzed data from 2,692 patients admitted to 28 centers in the Pediatric Collaborative Network of Latin America Acute Respiratory Failure Registry. Among patients referred from another facility (773, 28%), nonurban transports were independently associated with mortality (adjusted odds ratio = 9.4; 95% confidence interval: 2.4–36.3).

Keywords
- patient transfer
- critical illness
- mortality
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Introduction

Latin America and the Caribbean correspond to 38 countries. In 2018, it projected a population of 211,914,301 for less than 19-year-old children, consisting 33% population of the region. The projected mortality rate for these children under 5 years of age for 2015 to 2020 is 19.1 per 1,000 and in 2018, 24.2% of the population was living on less than $5.50 a day (at 2011 international prices).[1]

Pediatric critical care is a limited resource in many parts of Latin America. Many countries have centralized intensive care units (ICUs) to allow for better resource allocation and to provide quality health care services. In this model, tertiary centers provide specialized care for large areas.[2] The core of this model, especially in pediatric intensive care, relies on adequate referral and transport of critically ill patients from local facilities to tertiary centers.[3–7]

Referral and transport of critically ill children require a highly specialized and organized system to ensure the safety and adequate timing of advanced care.[8–11] However, information about referral and transport of critically ill children is scarce, especially in Latin America, where the health system organization is very diverse, even within the same country.[12,13] Critical care is a crucial step in the management of acutely ill children. We urgently need to better understand the many factors involved in providing a high quality of care. In addition, we need to identify high-risk groups, to propose efficient interventions to improve the outcomes of the critically ill children.

Given that respiratory failure is the main reason for admission to pediatric ICUs (PICUs),[14] our objective was to describe the characteristics of critically ill children admitted to PICUs after referral from an external facility by analyzing the Pediatric Collaborative Network of Latin America (LARed Network) acute respiratory failure registry. Furthermore, we aimed to investigate the association of referral and interfacility transport of critically ill children and clinical meaningful outcomes like mortality and length of stay (LOS).

Patients and Methods

Data Source

The LARed Network registry is a voluntary benchmarking and quality improvement collaborative for Latin American PICUs at 34 centers. Our analysis included data from 28 centers that were actively submitting data at the time of the study. The LARed Network registry dataset provides information on acute respiratory failure admissions, including patient characteristics, diagnosis, microbial etiology, respiratory support, and outcomes during PICU stay. A web-based case report form[15] is submitted to the core database, and a real-time feedback report with aggregated data of main quality indicators is given to each PICU. The LARed network registry qualifies as a quality improvement activity for each unit and is therefore not subject to ongoing institutional review board oversight. The data coordination center's institutional review board at Hospital San José, Bogotá DC, Colombia, provided a waiver of informed consent for this study.

Data Extraction

All cases submitted to the LARed Network registry between May 1, 2017 and October 1, 2018, were eligible for inclusion. Data extraction from the registry included demographic and clinical data including respiratory comorbidities (i.e., bronchopulmonary dysplasia, chronic lung disease, asthma or recurrent wheezing, others) and other comorbidities (i.e., heart disease, prematurity, malnutrition, genetic or neurological disorder, others), disease severity scores, pediatric index of mortality 3 (PIM3) score,[16] respiratory severity given by the modified Wood's Clinical Asthma Score (M-WCAS),[17] and arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio.

Outside facility referral was defined as any patient admitted to a PICU from another facility including any emergency room (ER), primary care, or specialty consult outside the referral hospital. Direct admission was defined as any patient who did not seek care at another health care facility before admission to PICU. Basically, the main difference of direct and outside referral is that the latter requires medical transport, even if it is 20 or 30 minutes due to a location in a separate facility, even if they both facilities belong to the same institution or network of hospitals. So, direct admission accounts for referral from the same hospital compound.

We further analyzed the subgroup of patients transferred from urban and nonurban areas. Those definitions were based on each center, according to their policies on urban limits. The primary outcome was PICU mortality. We calculated standardized mortality ratios (SMR) using observed deaths and expected deaths from PIM3 score. Secondary outcomes were maximal respiratory support (noninvasive positive pressure ventilation [NIPPV], such as continuous positive airway pressure [CPAP]/bilevel positive airway pressure [BiPAP]/high-flow nasal cannula [HFNC]) and PICU (LOS).

Statistical Analysis

This is a retrospective cohort study within a prospective collected registry. Descriptive statistics are provided as median and interquartile range (IQR) for continuous variables and as proportions (%) for categorical data. For bivariate analysis between the groups, referral versus direct admission, and nonurban versus urban areas, a nonparametric Kruskal–Wallis test was performed for continuous variables and a Chi-square test for categorical variables. All statistically significant variables from the bivariate analysis were introduced in a penalized logistic regression for referral versus direct admission analysis to adjust for potential confounders. All analyses were performed in STATA version 13.1 (Stata Corp, College Station, Texas, United States). We considered a value of $p < 0.05$, or a Bonferroni's correction when required, to be statistically significant.

Results

During the study period, data from 2,692 patients (58% male) were entered into the registry. Of those, 773 children (28%) were referred to the participating PICUs from another facility. Patient demographic and clinical characteristics are shown in ►**Table 1**. The median age for all patients was 7.4

Table 1 Demographic comparisons of direct admission patients and patients transferred from outside facilities

Characteristic	Direct admission ($n = 1{,}914$)	Transfer ($n = 773$)	p-Value
Age (mo) Median (IQR)	7.8 (2.9–18.7)	6.5 (2.3–21.2)	0.09
Weight (kg) Median (IQR)	8.0 (5.3–11)	7.5 (5–11.5)	0.16
Male sex *n* (%)	1,114 (58)	443 (57)	0.74
Comorbidities (all) *n* (%)	951 (50)	345 (45)	0.02
Respiratory[a]	674 (35)	235 (30)	0.02
Nonrespiratory[b]	527 (28)	198 (26)	0.31
Urban area residency *n* (%)	1,779 (93)	583 (76)	<0.01
Severity at admission Median (IQR)			
SaO_2/FiO_2	225 (164–335)	240 (163–336)	0.70
PaO_2/FiO_2	231 (150.5–329)	202 (127–300)	<0.01
M-WCAS	4.5 (4.0–5.5)	4 (3.5–5.5)	0.00
PIM3 (%)	0.49 (0.21–1.69)	0.39 (0.18–1.76)	0.08
Admission diagnosis *n* (%)			
Bronchiolitis	924 (48)	417 (54)	0.10
Pneumonia	562 (29)	174 (23)	0.06
Asthma	302 (16)	122 (16)	1.000
Other	123 (6)	59 (8)	0.29
Outcomes			
PICU LOS (d) Median (IQR)	4.3 (2.8–6.9)	4.8 (3.1–7.8)	<0.01
Mortality (observed) *n* (%)	21 (1)	14 (2)	0.14
Mortality (expected) *n* (%)	43 (2)	25 (3)	0.14
SMR Mean (95% CI)	0.49 (0.32–0.93)	0.57 (0.31–3.74)	
Maximal respiratory support *n* (%)			
Room air	7 (0)	4 (1)	0.58
Oxygen therapy only	184 (10)	108 (14)	<0.01
HFNC	517 (27)	355 (46)	<0.01
CPAP	81 (7)	49 (54)	0.02
BiPAP	601 (31)	40 (5)	<0.01
IMV	524 (27)	217 (28)	0.72

Abbreviations: BiPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; FiO_2, fractional inspired oxygen; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; M-WCAS, modified Wood's clinical asthma score; PaO_2, arterial oxygen partial pressure; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3; SaO_2, oxygen saturation; SMR, standardized mortality ratio.

Note: Group comparisons were made by chi-square tests (Fisher's test for less than five events per cell or Pearson's test for others) or nonparametric tests (Mann–Whitney/Kruskal–Wallis), depending on the type of variable; $p \leq 0.05$ was considered statistically significant.

[a]Bronchopulmonary dysplasia, chronic lung disease, asthma or recurrent wheezing, and others.

[b]Heart disease, prematurity, malnutrition, genetic or neurological disorder, and others.

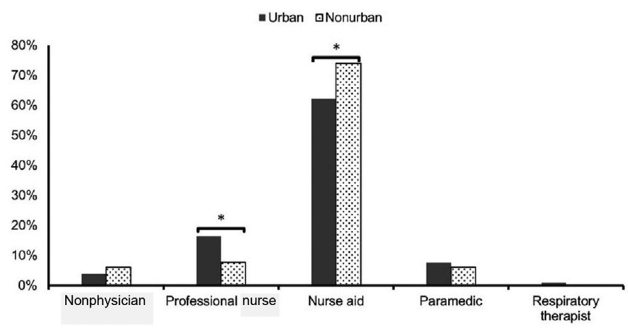

Fig. 1 Health care personnel carrying out transport of critical ill children from urban and nonurban centers. Individual caparisons were made by Chi-square using Pearson's or Fisher's test, one patient could be transferred with one or more personnel. $^{*}p \leq 0.05$ considered statically significant. Nonphysician category refers to any transport team where physician was not present.

months (IQR: 2.7–19.6 months), and median weight was 8 kg (IQR: 5.2–11 kg). The most frequent admission diagnoses for the cohort were bronchiolitis (50%), community-acquired pneumonia (27%), and status asthmaticus (16%). When we compared direct and referral admission groups, the referral group had a significantly lower PaO_2/FiO_2 ratio and M-WCAS, and significantly fewer respiratory comorbidities. There were no other significant differences between groups.

Characteristics of Transport for Referrals

Ground transport accounted for 98% of the referrals, with a median distance of 10 km (IQR: 7–90 km) and duration of 1 hour (IQR: 0.5–2.0 hours). Only 15 patients were transported by air, with a median distance of 687 km (IQR: 200–687 km) and a median duration of 2 hours (IQR: 2–3 hours). Health care personnel involved in transports were a physician and nurse assistant (66% of cases), physician (17%), physician and nurse (10%), and no physician (5%) (►**Fig. 1**). Respiratory support during transport was provided by nasal cannula (32%), oxygen mask (27%), HFNC (21%), CPAP (3%), BiPAP (3%), and invasive mechanical ventilation (14%).

Characteristics of PICU Stay for Referral and Direct Admission

When we compared the maximal respiratory support used during PICU stay between groups, HFNC was used more frequently in the referral group than in the direct admission group (46 vs. 27%; $p < 0.01$), whereas BiPAP was used more frequently in the direct admission group (31 vs. 5%; $p < 0.01$). The use of invasive mechanical ventilation was similar in the referral and direct admission groups (27 vs. 24%, respectively; ►**Table 1**). Mortality was 2% in the referral group and 1% in the direct admission group ($p = 0.14$). Standardized mortality ratio (mortality observed vs. expected) was 0.57 (IQR: 0.31–0.74) in the referral group and 0.49 (IQR: 0.32–0.93) in the direct admission group ($p = 0.14$). PICU LOS was 4.8 days (IQR: 3.1–7.8) in the referral group and 4.3 days (IQR: 2.8–6.9) in the direct admission group ($p < 0.01$).

Clinical and Transport Characteristics of Urban and Nonurban Referrals

When we compared urban and nonurban referrals, patients referred from urban areas had a significantly lower SaO_2 (oxygen saturation)/FiO_2 ratio at admission, but no other demographic or clinical differences were found. Air transport was more frequent from nonurban than from urban areas. We did not find differences in the traveled distance or "in-route" time between the two groups (►**Table 2**). We did find significant differences in staff for transport between urban and nonurban groups: nurses more frequently were involved in urban transports (16% urban vs. 8% nonurban; $p < 0.01$), whereas nurse assistants were more common in nonurban transports (62% urban vs. 74% nonurban; $p < 0.01$). Of note, presence of physician during transport was not different between groups (►**Table 3**). Mortality was significantly higher in the nonurban (5%) than in the urban referral group (1%; $p < 0.01$).

Multivariable regression analysis showed that nonurban referrals (odds ratio [OR] = 3.1; 95% confidence interval [CI]: 1.4–7.3), PIM3 score (OR = 1.05; 95% CI: 1.04–1.07), and comorbidities (OR = 3.5; 95% CI: 1.5–8.0) were independently associated with mortality, whereas a higher SaO_2/FiO_2 ratio (OR = 0.995; 95% CI: 0.991–0.999) at admission was associated with survival (►**Table 3**).

Discussion

In this study of the LARed registry, we described the clinical and transport characteristics of critically ill children transferred from an outside facility. Over one-fourth of children with acute respiratory failure were admitted to a PICU from another facility, and one-fourth of them came from nonurban areas. Strikingly, we found that referral from a nonurban area happened to be independently associated with mortality.

Although demographics were similar in the direct admission and referral groups, we found significant differences in diagnosis and maximal respiratory support. Mortality of the whole cohort was low, in accordance with selection criteria. There was a trend in higher morality in referral group compared with direct admission, and in the former also, there was a small increase in PICU LOS. Our findings are consistent with reports from developed regions, such as Europe and North America, where transferred patients have poorer clinical outcomes than direct admissions, even when adjusted by severity scores.[5,8,18–21] We found very few studies that compared transfer patients against direct admissions in Latin America. A systematic review by the Pan American Health Organization (PAHO) of neonatal transport in developing countries stated that children born in primary care or the community have higher mortality and morbidity than those born in health care centers with mother and child care.[22] In this review, only one study from Latin America was cited. In that 2011 paper, Araújo et al[23] compared premature babies who required transport to those assisted in a maternity center. They found greater mortality in those that were transferred (18 vs. 8.9%; risk ratio [RR] = 2.0; 95% CI:

Table 2 Comparisons of critically ill children admitted by transport from urban and nonurban centers

Demographics	Urban ($n=583$)	Nonurban ($n=187$)	*p*-Value
Age (mo) Median (IQR)	7 (2.5–21.4)	5.4 (2.0–20.2)	0.20
Weight (kg) Median (IQR)	7.6 (5.1–11.5)	7 (4.5–11.8)	0.08
Male sex *n* (%)	345 (59)	96 (51)	0.06
Comorbidities (all)[a] *n* (%)	260 (45)	83 (44)	0.96
Respiratory[a]	181 (31)	52 (28)	0.40
Nonrespiratory[a]	145 (25)	53 (28)	0.35
Admission diagnosis *n* (%)			
Bronchiolitis	323 (32)	93 (50)	0.24
Pneumonia	128 (22)	46 (25)	0.39
Asthma	92 (9)	30 (16)	0.78
Other	39 (4)	18 (10)	0.25
Interfacility transport			
Distance from center (km) Median (IQR)	10 (5–75)	10 (8–104)	0.08
Transfer duration (h) Median (IQR)	1 (0.3–2.0)	0.5 (0.5–2.0)	0.21
Air transport *n* (%)	7 (1)	8 (4)	<0.01
Land transport *n* (%)	576 (99)	179 (96)	
Respiratory support during transport *n* (%)			
Ambient or oxygen therapy	350 (60)	109 (58)	0.63
NIMV	149 (26)	54 (29)	
IMV	84 (14)	24 (13)	
Severity at admission Median (IQR)			
SaO_2/FiO_2	243 (165–336)	213 (157–327)	<0.01
PaO_2/FiO_2	208 (130–298)	170 (92–302)	0.21
M-WCAS	4 (3.5–5.5)	4 (3.5–5.5)	0.66
PIM3 (%)	0.4 (0.2–2.0)	0.4 (0.2–1.4)	0.50
Outcomes			
PICU LOS (d) Median (IQR)	4.9 (3.1–7.7)	4.7 (3.3–8.0)	0.87
Mortality (observed) *n* (%)	5 (1)	9 (5)	<0.01
Mortality (expected) *n* (%)	20 (3)	5 (3)	0.81
SMR Mean (95% CI)	0.25 (0.09–0.56)	1.80 (0.88–3.30)	<0.01
Maximal respiratory support *n* (%)			
Room air	4 (1)	0 (0)	0.29
Oxygen therapy only	92 (16)	16 (9)	0.12
HFNC	257 (44)	96 (51)	0.19
CPAP	39 (7)	10 (54)	0.42
BiPAP	35 (6)	4 (2)	0.15
IMV	156 (27)	61 (33)	0.21

Abbreviations: BiPAP, bilevel positive airway pressure; CI, confidence interval; CPAP, continuous positive airway pressure; FiO_2, fractional inspired oxygen; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; M-WCAS, modified Wood's Clinical Asthma Score; NIMV, noninvasive mechanical ventilation (HFNC and CPAP and BiPAP); PaO_2, arterial oxygen partial pressure; PICU, pediatric intensive care unit; PIM3, pediatric index of mortality 3; SaO_2, oxygen saturation; SMR, standardized mortality ratio.
Note: Group comparisons were made by chi-square tests (Fisher's test for less than five events per cell or Pearson for others) or nonparametric tests (Mann–Whitney/Kruskal–Wallis), depending on the type of variable; $p \leq 0.05$ was considered statistically significant.
[a]One patient can have more than one comorbidity.

Table 3 Multivariable logistic regression model investigating risk factors for death

Variable	aOR	95% CI
Transport	1.46	0.67–3.21
Nonurban transport	3.14	1.36–7.28
PIM3	1.05	1.04–1.07
SaO_2/FiO_2	0.99	0.99–0.99
Comorbidities	3.50	1.52–8.04

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; FiO2, fractional inspired oxygen; PIM3, pediatric index of mortality 3; SaO2, oxygen saturation.
Note: Data presented after fitting a logistic regression model for mortality using clinically relevant or statistically significant variables.

1.0–2.6), as well as higher rates of complications such as hyperglycemia (RR = 3.2; 95% CI: 2.3–4.4), hypoglycemia (RR = 2.4; 95% CI: 1.4–4.0), hyperthermia (RR = 2.5; 95% CI: 1.6–3.9), and hypoxemia (RR = 2.2; 95% CI: 1.6–3.0). There is insufficient data to explain these observations, but probably many factors are implicated. For instance, a significant issue is time to referral and treatments on the referral center. Referring physician has to weight the benefit and risks of an interfacility transfer for unstable patients, according to local available interventions (i.e., artificial airway). On the other way, facing limited resource settings, a low threshold for referral may lead to long waiting periods and overcrowding of tertiary care centers.

Importantly, we found that pediatric transfers from nonurban areas in Latin America were associated with a significant higher mortality. There is a significant gap in most of the health indicators between urban and nonurban areas, and these differences are especially large in low- and middle-income countries. The economic inequality in Latin America is a booster to put on the stage of disparities on the health indicators,[24–27] that is, the infant mortality rate can be 10 times higher between two locations within the same country.[28] Our finding regards the higher mortality of referrals from nonurban areas compared with urban areas, probably is a marker of all these socioeconomic aspects. Thus, these differences are likely due to a combination of factors, including poverty, limited access to health care services, and quality of transport, among others.

These data support findings in other world regions, and highlight the need to create specialized transport services, guidelines, and protocols for critically ill patients.[5,11,18,29–33] Transports were usually short distances, with an in-route time of 60 minutes, and ground transport was the most common modality. Moreover, the distance for nonurban transport was no longer than that for urban transport. We believe that the poorer clinical outcomes in the nonurban group can be explained by the fact that living in a nonurban area might be a marker for poverty and poor access to health services.

Surprisingly, physician participation during the transport was very common, but only a small proportion of transports included a nurse and respiratory therapist on the transport team. This observation mirrors the number of health care professionals in Latin America where nurses and respiratory therapists are very limited.[34] We were not able to determine the level of specialization of the transport team, or if there was a dedicated service of critically ill children. Nevertheless, our study has important similarities to and differences from previous work in pediatric transport. In 2001, Orr et al[35] showed that transport of pediatric patients in Pittsburgh by specially trained teams was associated with a lower incidence of unplanned events such as airway-related events, cardiopulmonary arrest, hypotension, and loss of crucial intravenous access, than was transport by nonspecialized teams (1.5 vs. 61%). After adjustment for illness severity, only the use of a nonspecialized team was independently associated with these unplanned events, and death was more common (specialized team: 9%; nonspecialized team: 23%). Another 4-year study of 29 PICUs in England and Wales showed that relocation by a specialized team increased the adjusted survival rate (OR = 0.6; 95% CI: 0.4–0.9). Still, the configuration of these teams varies considerably between institutions and regions.[18] The team composition may depend on the volume of patients transferring, the age of the patient, the type of pathology, type of transfer (air or land), and academic training. Some researchers have suggested use of a pediatric transport triage tool to standardize for these variations.[33]

The American Academy of Pediatrics and the Second National Leadership Conference in Pediatric and Neonatal Interface Transport Medicine recommend the presence of at least one nurse on the transport team.[36,37] Compared with other team members, professional nurses have particularly useful skills for clinical evaluation, laboratory and image interpretation, and procedures, highlighting the importance of their role on the team.[38] In Ibero-America, few studies have examined the use of specialized transfer teams. De la Mata et al,[13] who conducted a survey on interhospital transport of pediatric and neonatal patients, showed that 36.7% of the transport personnel were pediatric nurses, but the study included Spain and Portugal. Our study showed much lower nurse participation. This may be due to low availability, as reported by the PAHO.[39]

Limitation

Our study is limited by the fact that we analyzed observational data of clinical registries. The LARed Network registry is subject to many levels of data integrity supervision by built-in algorithms in the on-line forms, but we cannot rule out the possibility that data may be missing due to nonreport of complex clinical information. As mentioned above, this registry does not include all variables that may affect outcomes of transferred patients, such as prehospital management, socioeconomic characteristics, en route clinical variables, and an in-depth description of health personnel and technology available during transport. Based on our design, we used only aggregated data as we were unable to analyze specific centers and countries without disclosing sensitive data. Overall, this limits our findings to regions with same demographics, types of transport, and personnel available.

Conclusion

In conclusion, transport for PICU referrals is frequent in Latin America, and nonurban transport is independently associated with mortality. Our findings emphasize the urgent need for collaboration at multi-institutional levels to measure and understand the regional context and real-world practices. This valuable insight can be used to improve the quality of care for critically ill children who are transferred from nonurban centers in Latin America.

Authors' Contributions
J.A.S. and F.D. equally contributed to this research as main authors. They were involved in planning and designing the study and participated in all stages of the project. F.D., J.A.S., and M.J.N. conceived the idea. F.D., J.A.B.S., N.M.F., S.G.D., C.C., and P.C. were involved in development of the data extraction questionnaire.
F.D. and P.V.H. analyzed the data and described the results. J.C.J.B., J.A.B.S., M.J.N., R.J., L.M.A., A.W., A.F., A.D., C.C., and S.R.K. contributed to the interpretation of the results.
J.A.S. took the lead in writing the manuscript in consultation with F.D., P.C., and A.D. J.A.B.S., J.C.J.B., A.F., L.M.A., L.P.O., C.Co, C.C., J.M., M.J.N., S.R.K., and S.M. contributed to the discussion in accordance with the results.
All authors were involved in data collection and manuscript preparation and provided critical feedback to the analysis and discussion.
F.D., J.A.S., P.V.H., and S.G.D. supervised the whole project. F.D., J.A.S., and P.V.H. are the guarantors of and take responsibility for the content of the manuscript. All authors have made substantial contributions to the research, provided

final approval of the version to be published, and have agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

Note

Patients admitted to pediatric intensive care units in Latin America for respiratory failure are frequently referred from an outside facility. In this study, we found an independent association between referral from nonurban areas and mortality. This valuable insight can be used to improve quality of care for critically ill children who are transferred from nonurban centers in Latin America.

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Conflict of Interest

None declared.

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