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Variability in care for children with severe acute asthma in Latin America

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Abstract

Background: Care variability for children with severe acute asthma has been well documented in high-income countries, yet data from low- and middle-income regions are lacking. We sought to characterize the magnitude of practice variability in the care of Latin American children to identify opportunities for standardization of care.

Methods: A cross-sectional study performed through a retrospective analysis of contemporaneously collected data of children with severe acute asthma admitted to a center contributing to the LARed Network registry between May 2017 and May 2019. Centers were grouped by geographic location: Atlantic (AT), South Pacific (SP), and North Central (NC).

Results: Among 434 children, most received care in hospitals in the AT group (54% [235/434]), followed by the NC (23% [101/434]) and SP (23% [98/434]) groups. The majority of children in the AT (92% [215/235]) and SP (91% [89/98]) groups received nebulized salbutamol/albuterol, while metered-dose inhalers were preferred in the NC group (72% [73/101]). There was a wide variation in the use of antibiotics: AT (57% [135/235]), SP (48% [47/98]), and NC (14% [14/101]). The same was true for ipratropium bromide: AT (67% [157/235]), SP (90% [88/98]), and NC (17% [17/101]), and aminophylline: AT (57% [135/235]), NC (5% [5/101]), and SP (0% [0/98]). High-flow nasal cannula was the preferred respiratory support modality in the AT (60% [141/235]) and NC (40% [40/101]) groups, while bilevel positive airway pressure (BiPAP) use was more common in the SP group (80% [78/98]).

Conclusion: We identified significant variability in care for severe acute asthma. Our findings will help to inform the design of future studies, quality improvement initiatives, and development of practice guidelines within Latin America.

KEYWORDS

asthma, asthma acute exacerbation, children, severe acute asthma, status asthmaticus

1 | BACKGROUND

Asthma is the most prevalent chronic disease in childhood, affecting 9.5% of all children in the United States.[1] Internationally, the prevalence of pediatric asthma varies broadly, from approximately 5% in some Asian and Eastern European countries to nearly 25% in parts of the United Kingdom, Oceania, and Latin America.[2] Even within Latin America, the prevalence of pediatric asthma is not uniform, varying between 3% and 27% depending on the geographic region.[3] Population-based rates of asthma hospitalizations appear to be decreasing,[4] yet the number of children requiring intensive care for the treatment of severe acute or critical asthma is on the rise.[5] Asthma is associated with a significant disease burden and has been identified as a research priority due to its high financial impact, prevalence, and variation in resource utilization.

While the long-term management of pediatric asthma predicated on symptom control, risk reduction, and treatment of acute exacerbations is well directed by expert panels,[6–9] guidelines for the management of children with severe acute asthma in the intermediate and intensive care settings are lacking. In the absence of well-established guidelines, clinical management is influenced by individual preferences and local practice, thus creating a potential vulnerability in the care of these patients in the more severe—and thus more unforgiving—end of the disease spectrum. Variability in the care of children with severe acute or critical asthma has been well documented in high-income countries,[10–15] yet the magnitude of this issue has not been described in low- and middle-income regions, like Latin America. If present, variability in care can be associated with under and overtreatment, misuse of resources, longer hospital stay, and higher costs.[14] It creates an opportunity for optimization of care through quality improvement efforts and evidence-based practice standardization.[11]

In this cross-sectional study, we sought to characterize the magnitude of practice variability in the care of children with severe acute asthma requiring intermediate or intensive care in Latin America. Our objective is to identify opportunities for benchmarking and standardization of care through the use of real-world data, and inform future research and quality improvement projects within the Latin American Pediatric Research Collaborative (LARed Network).

2 | PATIENTS AND METHODS

2.1 | Setting and data source

The LARed Network is a research collaborative currently composed of 40 hospitals caring for children in various Latin American countries. It maintains a contemporaneously acquired acute respiratory failure (ARF) data registry which started in 2014 and was built using a Redcap Software platform.[16] The registry collects epidemiological information on pediatric admissions due to ARF in patients up to 14 years of age and is described in greater detail elsewhere.[17]

For this study, we included 29 institutions from seven countries in Latin America (Argentina, Bolivia, Chile, Colombia, Costa Rica, Ecuador, and Uruguay) that actively participated in the LARed ARF registry for the entire study period.

2.2 | Study design and participants

We conducted a cross-sectional study using retrospective analysis of contemporaneously recorded data from the LARed Network ARF clinical registry that included all cases submitted between May 1, 2017 and May 1, 2019. We included all cases with a primary admission diagnosis of severe acute asthma in children older than 2 years of age admitted to an intermediate care unit or to a pediatric intensive care unit (PICU). Entries with incomplete data were excluded from the analysis.

2.3 | Variables

We extracted relevant demographic and clinical data, including age, weight, sex, ethnicity, country, hospital type, admission origin, admission site, comorbidities, pharmacological treatments, respiratory support, length of stay, mortality, and disease severity scores (i.e., Pediatric Index of Mortality 3 [PIM3] score and Modified Wood's Clinical Asthma score [M-WCAS]). Patients were admitted either to an intensive or to an intermediate care unit. The level of care categorization is determined by each center according to country regulations. An intensive care unit follows the same principles and operations of a PICU in North America. An intermediate care unit is a dedicated patient care area capable of providing immediate resuscitation and short-term cardiorespiratory support; it is also used as a site for monitoring "at risk" medical and surgical patients for possible deterioration. An intermediate care unit must be capable of providing noninvasive or even invasive mechanical ventilation and simple cardiovascular monitoring for a period of at least several hours. We also collected treatment data, including the use of corticosteroids, short-acting β-agonists (SABAs), ipratropium bromide, methylxanthines, magnesium sulfate, antibiotics, and respiratory support modalities (i.e., high-flow nasal cannula [HFNC], continuous positive end-expiratory pressure [CPAP], bilevel positive airway pressure [BiPAP], and invasive mechanical ventilation [IMV]). Outcome variables included PICU length of stay and mortality.

2.4 | Data analysis

Data are presented as medians and interquartile ranges (IQRs) for continuous variables, as they were non-normally distributed (Shapiro–Wilk test), and proportions (%) for categorical variables. Institutions were clustered by geographic location into three groups: (1) Atlantic (AT), Uruguay, and Argentina; (2) South Pacific (SP), Chile; and (3) North Central (NC), Bolivia, Colombia, Ecuador, and

Costa Rica. Comparisons among the geographical groups were performed using the Kruskal–Wallis one-way analysis of variance on ranks (continuous data) or a X^2 test (categorical data) with post hoc using Pearson adjusted residuals or a Dunn test with Bonferroni correction for multiple comparisons.

All analyses were performed using STATA Version 13.1 (Stata Corp). Statistical significance was defined as $p < .05$. This study was approved by and conducted under the oversight of the data coordinating center's Institutional Review Board (Hospital San José) with a waiver of informed consent.

3 | RESULTS

During the study period, a total of 3551 subjects were entered into the LARed ARF registry (Figure 1). Out of those, 434 (12%) patients were over the age of 2 years and had an admission diagnosis of severe acute asthma; the frequency of this diagnosis among the 29 participating centers varied from 0% to 23%.

The majority of patients were younger than 12 years of age (94%; 408/434), female (53%; 230/434), and identified as Caucasian (68%; 295/434; Table 1). A total of 46% (199/434) of subjects were treated at academic hospitals, 40% (175/434) received care at public institutions, and 38% (163/434) were transferred from another facility. The PICU was the admission site for 36% (158/434) subjects, while the remaining 64% (276/434) were admitted to an intermediate care unit.

Pre-existing respiratory comorbidities, such as broncho-pulmonary dysplasia, chronic lung disease, and bronchiolitis obliterans, were present in 29/434 subjects (7%). Three patients were receiving oxygen support at home before admission, and none of the patients had a tracheostomy or were receiving long-term mechanical ventilation before admission. As expected, the PIM3 score was low (0.23 [0.15–0.47]) while the M-WCAS score (5 [4–5.5]) indicated that patients had moderate to severe disease severity and impending respiratory failure. The median length of stay in the treatment unit was 3 [2–4] days. There were no deaths (Table 1).

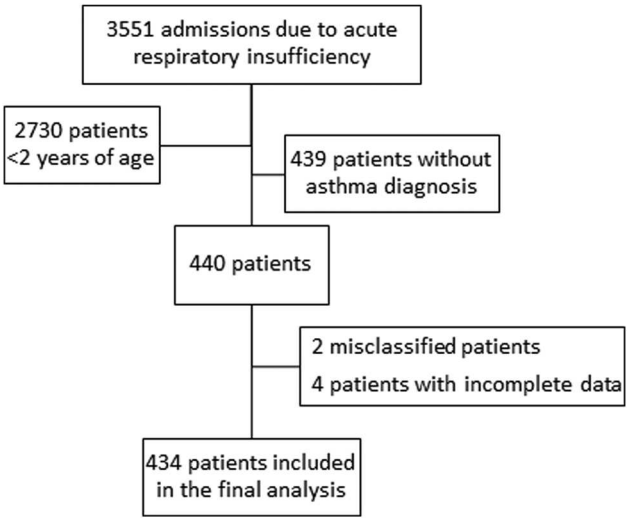

FIGURE 1 Patient flow diagram

Most subjects in our sample originated from hospitals in the AT group (54%; 235/434), followed by the NC (23%; 101/434) and SP (23%; 98/434) groups. The relative contribution of each hospital to the entire cohort within their geographic group is shown in Figure 2.

As expected, the vast majority of subjects were treated with corticosteroids (96%; 418/434) and SABAs (98%; 424/434; Table 2). There was a wide variation in the choice of corticosteroid drug, with hydrocortisone being more commonly used in the AT (89%; 209/235) and SP (88%; 86/98) groups, while prednisone was preferred in the NC group (65%; 66/101). The same was true for the administration of SABAs, with nebulized salbutamol (albuterol) being the most common route in the AT (92%; 215/235) and SP (91%; 89/98) groups, while metered-dose inhalers were preferred in the NC group (72%; 73/101). The use of intravenous β-agonists was low across all regions and there was no report of continuous albuterol nebulization.

A total of 45% (196/434) of subjects received treatment with antibiotics for a suspected bacterial respiratory infection. The most commonly prescribed antibiotics were a macrolide in 21% (42/196) of patients, or penicillin in 18% (35/196). Fifty-seven patients received two antibiotics, with the most common combination being a macrolide and a β-lactam agent (9%; 5/57). A third-generation cephalosporin was prescribed in 19/434 (4%) patients. Antibiotic use was much more frequent in the AT (57%; 135/235) and SP (48%; 47/98) groups compared to the NC group (14%; 14/101).

There was wide variability in the use of ipratropium bromide and aminophylline. The administration of ipratropium bromide was much more common in the AT (67%; 157/235) and SP (90%; 88/98) groups compared to the NC group (17%; 17/101; Table 2). Aminophylline was used in 32% (140/434) of the entire cohort, and was mostly used in the AT group (57%; 135/235), contrasting to the relatively low use in the NC (5%; 5/101) and SP (0%; 0/98) groups. The use of magnesium sulfate in the entire cohort was 19% (82/434), with a fairly uniform use among the three regions (Table 2). The variability in the use of medications among the three regions is shown in Figure 3.

Most patients (84%; 366/434) received some form of respiratory support beyond a simple nasal cannula or oxygen via facemask. The most commonly used support modalities were HFNC (43%; 185/434), BiPAP (26%; 111/434), and CPAP (10%; 43/434; Table 3). There was wide variability in the choice of respiratory support among the geographic groups. While HFNC was the preferred support modality in the AT (60%; 141/235) and NC (40%; 40/101) groups, BiPAP was most commonly used in the SP group (80%; 78/98; Table 3). IMV was used in 27 patients (6%; 27/434). These patients had a higher M-WCAS (5 [4–5.5] vs. 6 [6–6.5], $p < .001$), higher use of intravenous magnesium sulfate (11/27 vs. 71/407, $p = .003$) and antibiotics (19/27 vs. 177/407, $p < .001$), and had a longer length of stay in the intermediate care unit or PICU (6 [4–8] days vs. 3 [2–4] days, $p < .001$) compared to patients treated with other respiratory support modalities, respectively.

TABLE 1 Characteristics and disease severity at admission by geographic region

Variable	All *n* = 434 (100%)		Atlantic (AT) *n* = 235 (54%)		North Central (NC) *n* = 101 (23%)		South Pacific (SP) *n* = 98 (23%)		*p*[a]
Age groups, *n* (%)									
Preschool-aged (2–5 years old)	219	(50%)	124	(53%)	47	(47%)	48	(49%)	.80
School-aged (6–11 years old)	189	(44%)	96	(41%)	48	(48%)	45	(46%)	
Teenager (≥12 years old)	26	(6%)	15	(6%)	6	(6%)	5	(5%)	
Weight, kg, median [IQR]	20	[15–29]	20	[15–28]	21	[15–30]	22	[16–34]	.72
Female sex, *n* (%)	230	(53%)	122	(52%)	64[b]	(63%)	44	(45%)	.03
Ethnicity, *n* (%)									
Caucasian	295	(68%)	207[b]	(88%)	7[b]	(7%)	81[b]	(83%)	<.01
Mestizo	135	(31%)	27[b]	(12%)	91[b]	(90%)	17[b]	(17%)	
African American	3	(1%)	1	(0%)	2	(2%)	0	(0%)	
Indigenous	1	(0%)	0	(0%)	1	(1%)	0	(0%)	
Hospital type, *n* (%)									
Academic (vs. nonacademic)	199	(46%)	10[b]	(4%)	101[b]	(100%)	88[b]	(90%)	<.01
Public (vs. private)	175	(40%)	49[b]	(21%)	28[b]	(28%)	98[b]	(100%)	<.01
Admission origin, *n* (%)									
Same hospital (internal)	271	(62%)	130[b]	(55%)	47[b]	(46%)	94[b]	(96%)	<.01
Other hospital (external)	163	(38%)	105[b]	(45%)	54[b]	(54%)	4[b]	(4%)	
Admission site, *n* (%)									
PICU	158	(36%)	86	(37%)	62[b]	(61%)	10[b]	(10%)	<.01
Intermediate care unit	276	(64%)	149	(63%)	39[b]	(39%)	88[b]	(90%)	
Comorbidities, *n* (%)									
Respiratory comorbidities[c]	29	(7%)	5[b]	(2%)	11	(11%)	13[b]	(13%)	<.01
Other comorbidities	88	(20%)	39	(17%)	19	(19%)	30[b]	(31%)	<.01
PIM3, median [IQR]	0.23	[0.15–0.47]	0.21[b]	[0.16–0.44]	0.15[b]	[0.14–0.23]	0.44[b]	[0.37–0.65]	<.01
M-WCAS, median [IQR][c]	5.0	[4–5.5]	5.5[b]	[4.5–6]	4[b]	[2.5–5]	5[b]	[4.5–5.0]	<.01
Length of stay, median [IQR]	3	[2–4]	3[b]	[2–5]	2	[2–4]	3	[2–4]	<.01
Mortality, *n* (%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	–

Abbreviations: IQR, interquartile range; M-WCAS, Modified Wood's Clinical Asthma score; PICU, pediatric intensive care unit; PIM3, Pediatric Index of Mortality 3 score.

[a] X^2 or Kruskal–Wallis test.

[b] $p < .05$ after Pearson residuals analysis and Bonferroni correction.

[c] Respiratory comorbidities include bronchopulmonary dysplasia, chronic lung disease, bronchiolitis obliterans.

[c] 386 subjects with data Modified Wood's Clinical Asthma score (M-WCAS) available for analysis.

4 | DISCUSSION

In this study of a multinational Latin American pediatric cohort, we identified significant variability in the care of children admitted with severe acute asthma across three geographic regions. Although the use of "front line" therapies, such as systemic corticosteroids and SABAs, was fairly uniform, there was still significant heterogeneity in the specific drug used or mode of delivery, and in the use of adjunct treatments. The latter included the disparate use of ipratropium bromide, aminophylline, antibiotics, magnesium sulfate, and choice of respiratory support. We showed that the significant variability in care observed among regions did not appear to affect clinical outcomes, such as length of stay, need for mechanical ventilation, or mortality, suggesting that opportunities exist to standardize care.

Although to our knowledge, this is the first large scale description of variability in the treatment of pediatric severe acute asthma in Latin America, heterogeneity in asthma care has been well described in high-income countries.[10–15] In the United States, Bratton et al.[12] described wide variability in therapies used to treat children with asthma admitted to eight PICUs participating in the Collaborative Pediatric Critical Care Research Network (CPCCRN) and in a sample of 40 children's hospitals that contribute data to the Pediatric Health Information System (PHIS) database. Wide practice variability was also shown in the more severe end of the pediatric

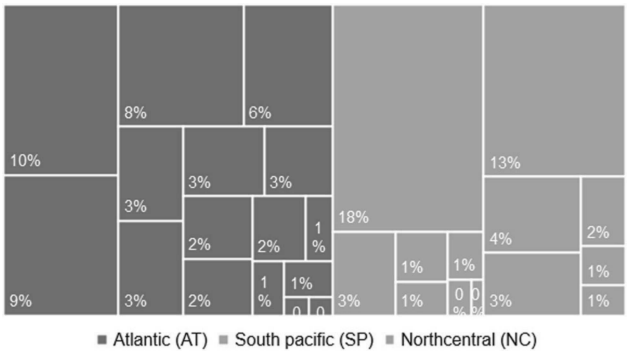

FIGURE 2 Tree map showing the relative contribution of cases from individual centers grouped by geographic location. Percentages represent the contribution within each group. Data from 29 centers are shown since 9 centers that did not have eligible cases during the study period were excluded [Color figure can be viewed at wileyonlinelibrary.com]

asthma spectrum by Newth et al.[15] in a study of 261 mechanically ventilated children within the CPCCRN network. In Europe, Lachaussée et al.[10] demonstrated a high variability in the treatment of children with severe cute asthma admitted to six PICUs serving approximately 40% of the French pediatric population. In that study, variability in clinical management was most pronounced in the use of intravenous β-agonists and magnesium sulfate.[10] More recently, Boeschoten et al.[13] reported significant heterogeneity in the treatment of children with severe acute asthma in a cross-sectional survey of 37 PICUs in 11 European countries, especially in the choice of adjunct therapies. Of note, nearly one in every four units lacked guidelines on the management of severe acute asthma.

Unsurprisingly, the vast majority of patients in our cohort received treatment with SABA (98%) and a systemic corticosteroid (96%). Considering these agents are the foundation of severe acute asthma treatment, one would expect that all, or nearly all, patients would have received both during the course of treatment. This expectation is underscored in the finding that all units surveyed by Boeschoten et al.[13] indicated using these drugs every time. However, not all patients received a β-agonist in the study by Bratton et al.,[12] and only approximately 85% of patients received a systemic corticosteroid.

We found significant variability in the use of antibiotics among regions in our sample. The use of an antibiotic was significantly higher in children treated in hospitals located in the AT and SP regions (57% and 48%, respectively) compared to those in the NC region (14%). We find it unlikely that the presence of a bacterial infection in children with severe acute asthma would be so disparate among regions, so it is likely that this variability in practice might be due to modifiable factors, like local practice patterns, family or provider expectation, or risk tolerance, among others. Considering that the use of antibiotics in a comparable North American sample was 39%,[12] our finding could present an opportunity for practice standardization.

We also found extreme variability in the use of ipratropium bromide and aminophylline in our sample. Ipratropium bromide has a well-defined role in the initial treatment of children with severe acute asthma in the emergency department[18,19] but its role in the inpatient

TABLE 2 Pharmacological therapies by region

Variable	All N = 434		Atlantic (AT) N = 235		North Central (NC) N = 101		South Pacific (SP) N = 98		p[a]
Corticosteroids[b]	418	96%	228	97%	94	93%	96	98%	.17
Hydrocortisone	300	69%	209[c]	89%	5[c]	5%	86[c]	88%	<.01
Methylprednisolone	37	9%	2[c]	1%	25[c]	25%	10	10%	<.01
Prednisone	103	24%	34[c]	15%	66[c]	65%	3[c]	3%	<.01
Salbutamol (albuterol)[d]	424	98%	235	100%	96[c]	96%	96	98%	<.01
Intravenous	13	3%	12[c]	5%	0	0%	1	1%	.02
Nebulized	333	77%	215[c]	92%	29[c]	29%	89[c]	91%	<.01
MDI	110	25%	30[c]	13%	73[c]	72%	7[c]	7%	<.01
Antibiotic	196	45%	135[c]	57%	14[c]	14%	47	48%	<.01
Ipratropium bromide	262	60%	157[c]	67%	17[c]	17%	88[c]	90%	<.01
Aminophylline	140	32%	135[c]	57%	5[c]	5%	0[c]	0%	<.01
Magnesium sulfate	82	19%	46	20%	15	15%	21	21%	.46

Abbreviation: MDI, metered-dose inhaler.

[a]Pearson's X^2 test.

[b]Some subjects received more than one type of corticosteroid.

[c]$p < .05$ after Pearson residuals analysis and Bonferroni correction.

[d]Some subjects received salbutamol (albuterol) through more than one route.

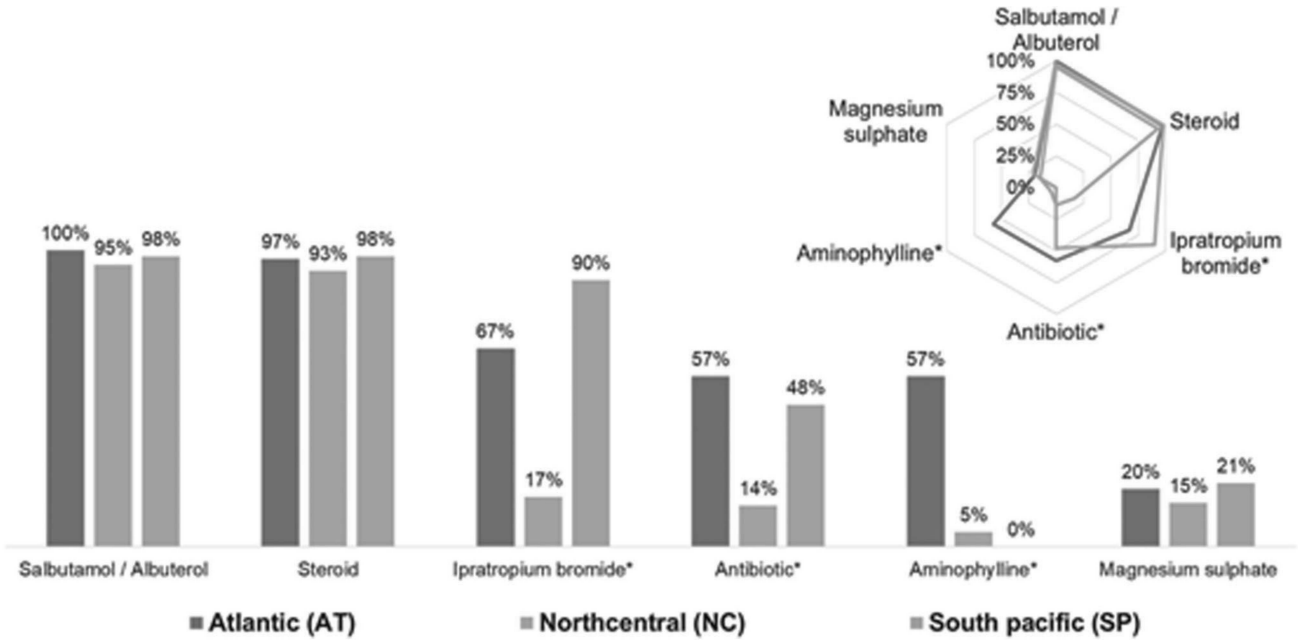

FIGURE 3 Radar and bar distribution of therapies prescribed in each group. *Note:* *denotes statistically significant differences among groups [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Highest level of respiratory support by region

Variable	All N = 434		Atlantic N = 235		North Central N = 101		South Pacific N = 98		p[a]
Nasal cannula	16	(4%)	8	(3%)	6	(6%)	2	(2%)	<.01
High flow facemask	52	(12%)	6[b]	(3%)	39[b]	(39%)	7	(7%)	
HFNC	185	(43%)	141[b]	(60%)	40	(40%)	4[b]	(4%)	
CPAP	43	(10%)	38[b]	(16%)	1	(1%)	4	(4%)	
BIPAP	111	(26%)	26[b]	(11%)	7[b]	(7%)	78[b]	(80%)	
Invasive ventilation	27	(6%)	16	(7%)	8	(8%)	3	(3%)	

Abbreviations: CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; HFNC, high-flow nasal cannula.

[a]Pearson's X^2 test.

[b]$p < .05$ for Pearson residuals analysis with Bonferroni correction.

setting is questionable.[20] It is, therefore surprising that 67% of children in the AT region and 90% of children in the SP region received this agent, in contrast to 17% in the NC region. It appears that, in the absence of data germane to the more severe end of the inpatient asthma spectrum, physicians might be relying on outpatient studies[18,19] coupled with the favorable side effect profile of ipratropium bromide to justify its use in this population. The same cannot be said for the high use of aminophylline in the AT region (57%) compared to the NC (5%) and SP (0%) regions. Aminophylline has a less favorable side effect profile, questionable efficacy, and is not recommended by expert guidelines,[6,8] so this variability in care presents another excellent opportunity for benchmarking and standardization.

The type of respiratory support also varied widely in our sample. While HFNC was the preferred support modality in the AT (60%) and NC (40%) regions, BiPAP was most commonly used in the SP region (80%). Although well established in the treatment of bronchiolitis[21–23] and undifferentiated adult respiratory failure,[24] robust data on the role of HFNC in severe acute asthma are lacking. The utility of BiPAP in children with severe acute asthma has been demonstrated in small interventional studies.[25,26] Therefore, the high variability in the choice of respiratory support in our sample suggests the presence of equipoise for the conduct of a prospective trial within our network that might help determine the equivalence or superiority of either modality. Regardless of the choice of respiratory support modality in our sample, the vast majority of patients (94%) showed clinical improvement and did not require invasive mechanical ventilation. Our mechanical ventilation rate of 6% is in line with comparable studies from Europe[10] and North America.[12]

The wide variability in care found in our study is not surprising, considering existing asthma care guidelines are not specifically focused on the more severe end of the spectrum of hospitalized children with severe acute asthma.[6–8] Adding to this challenge is the fact that the existing national and international guidelines for asthma care show a relatively low degree of agreement.[27]

Our study has significant strengths; it included a relatively large sample of children with severe acute asthma treated in 29 hospitals across Latin America in an attempt to characterize variability in care. We believe it provides a snapshot of real-world data reflecting the types of treatments dispensed to these children across a vast and heterogeneous continent. Our study also has weaknesses; all participating hospitals are part of a collaborative network created to facilitate the sharing of information and practices, so it may not be appropriate to generalize our findings to nonnetwork hospitals. However, we believe the risk of selection bias is attenuated by the fact that our network has a good balance between academic and nonacademic centers, as well as private and public hospitals. Another important limitation is the lack of complete clinical data before hospital admission, especially regarding treatments and interventions performed at a referring hospital for patients who originally presented to another facility (38% of our sample). It is impossible for us to determine the relative contribution of individual factors to the wide variability of care observed in our study. It is possible that some of the care variability could have been attributable, at least in part, to differences in disease severity. We believe this not to be a significant issue since our sample had fairly uniform asthma severity scores upon admission. It is more likely that variability in care was in fact due to patterns rooted in local or regional medical practice styles, or dictated by the nonuniform availability of materials, staffing, and infrastructure among centers.

In conclusion, we described the clinical characteristics of children with acute severe asthma admitted to a diverse collection of hospitals in Latin America, and identified significant variability in care, particularly as it pertains to adjunct therapies. Our findings will help inform the design of future international collaborative studies within Latin America, which may fill knowledge gaps in what constitutes best practices for the treatment of acute severe asthma in the region. We also hope to have identified opportunities for the development of quality improvement initiatives and clinical practice guidelines that might decrease practice variability, improve quality of care, optimize resource allocation, and maximize the value in the care we deliver in Latin America.

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CONFLICT OF INTERESTS

Dr. Rotta is a scientific advisor for Breas Medical and Vapotherm and has received honoraria for the development of educational materials and lecturing. The remaining authors do not have conflict of interests to disclose.

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