

Therapeutic variability in infants admitted to Latin-American pediatric intensive units due to acute bronchiolitis

Variabilidad terapéutica en lactantes con bronquiolitis hospitalizados en unidades de cuidados intensivos latinoamericanas

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Received: 28 de marzo de 2019; Approved: 23 de noviembre de 2019

What do we know about the subject matter of this study?

Based on current evidence, the recommended management of acute bronchiolitis is supportive therapy. However, different therapies without scientific evidence are frequently used, which may be potentially harmful to patients and health systems.

What does this study contribute to what is already known?

This multicenter study in 20 pediatric intensive care units in five Latin American countries shows high variability in the therapies used in acute bronchiolitis and a lack of adherence to current recommendations. This study uncovers an important issue in Latin America, showing an opportunity for improvement in patient management, with effects on the management of clinical and economic resources of the health systems.

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How to cite this article: Rev Chil Pediatr. 2020;91(2):216-225. DOI: 10.32641/rchped.v91i2.1156

Abstract

The objective of this study was to describe the management of infants with acute bronchiolitis admitted to 20 pediatric intensive care units (PICU) members of LARed in 5 Latin American countries. **Patients and Method:** Retrospective, multicenter, observational study of data from the Latin American Registry of Acute Pediatric Respiratory Failure. We included children under 2 years of age admitted to the PICU due to community-based acute bronchiolitis between May and September 2017. Demographic and clinical data, respiratory support, therapies used, and clinical results were collected. A subgroup analysis was carried out according to geographical location (Atlantic v/s Pacific), type of insurance (Public v/s Private), and Academic v/s non-Academic centers. **Results:** 1,155 patients were included in the registry which present acute respiratory failure and 6 were excluded due to the lack of information in their record form. Out of the 1,147 patients, 908 were under 2 years of age, and out of those, 467 (51.4%) were diagnosed with acute bronchiolitis, which was the main cause of admission to the PICU due to acute respiratory failure. The demographic and severity characteristics among the centers were similar. The most frequent maximum ventilatory support was the high-flow nasal cannula (47%), followed by non-invasive ventilation (26%) and invasive mechanical ventilation (17%), with a wide coefficient of variation (CV) between centers. There was a great dispersion in the use of treatments, where the use of bronchodilators, antibiotics, and corticosteroids, representing a CV up to 400%. There were significant differences in subgroup analysis regarding respiratory support and treatments used. One patient of this cohort passed away. **Conclusion:** we detected wide variability in respiratory support and treatments among Latin American PICUs. This variability was not explained by demographic or clinical differences. The heterogeneity of treatments should encourage collaborative initiatives to reduce the gap between scientific evidence and practice.

Keywords:

bronchiolitis;
respiratory failure;
respiratory syncytial virus;
therapeutic variability;
pediatrics;
critical care;
Latin-America

Introduction

The leading infectious cause of infant mortality in Latin America is acute respiratory failure. Despite this, there is very little information on the different etiologies and clinical syndromes causing respiratory failure, specifically acute bronchiolitis and respiratory syncytial virus (RSV) pneumonia, and their impact on morbidity and mortality, health system and resources used in the region¹⁻⁷. Acute bronchiolitis is a low-lethality disease, but there are groups of patients with specific comorbidities that have been recognized as risk factors for developing severe acute bronchiolitis^{8,9}.

Acute bronchiolitis has an impact on health systems, and it is the main cause of hospitalization and admission to Pediatric Intensive Care Units (PICU) during winter seasons in different regions worldwide, with the costs associated that this implies¹⁰. In the last decade, there has been a growing trend in the number of PICU admissions due to this pathology, with a marked seasonal and regional variation¹¹⁻¹³.

Although multiple drug therapies have been tested, there are currently no specific etiological or symptomatic treatments for acute bronchiolitis. According to the current evidence, most of the available therapies are ineffective. Pediatric scientific societies in North America, Europe, and Latin America have published a set of updated guidelines for acute bronchiolitis¹⁴⁻¹⁷ emphasizing that treatment is supportive, where oxygen the-

rapy and hydration are the only relevant interventions agreed upon¹⁷⁻²¹.

Given the lack of specific therapies, there is great variability of treatments, an often invisible, globally widespread, and poorly reported phenomenon. This phenomenon is especially relevant in severe acute bronchiolitis where, in the face of clinical deterioration, many children receive useless therapies not supported by evidence, and even with a potentially negative effect on the course of the disease²²⁻²⁴. This variation leads to the inadequate use of diagnostic and therapeutic tools, increasing costs and worse clinical outcomes.

The objective of this study is to characterize and analyze the variability of therapeutic interventions administered to infants admitted to PICU with diagnosis of acute community-acquired bronchiolitis in 20 pediatric centers in five Latin American countries. Our hypothesis is that there is a great heterogeneity of respiratory support and therapies used in infants with acute community-acquired bronchiolitis.

Patients and Method

Retrospective study using data prospectively collected of 20 PICU members of LARed Network. LARed Network is a collaborative initiative of PICUs²⁵ that promotes the Latin American Registry of Pediatric Acute Respiratory Failure. This registry comprises a

single standardized online form using REDCap® software²⁶. The patient records included in LARed has *de-identified data* (all personally identifiable information has been removed) and they were replaced by an automated identifier number provided by the software. Standardized and quality metrics with real-time feedback to the participating centers were used for benchmarking.

Registry data were collected and managed using the REDCap® electronic data capture software hosted on servers at Facultad de Medicina, *Clínica Alemana, Universidad del Desarrollo* (26). REDCap® is a secure, web-based system designed to allow data collection for records, which provides 1) an intuitive interface for entering validated data, 2) audit trails to track manipulation and export data procedures, 3) automated export procedures for continuously data downloads to common statistical packages, and 4) procedures for importing data from external sources.

The participation of all centers was approved by the local Scientific Ethics Committee (SEC). If the centers did not have an accredited SEC, as occur in private centers in Uruguay and Bolivia, they presented the institutional authorization for the use of external accredited CEC approval.

Out of the total number of patients with acute respiratory failure, the following criteria were considered for definitive inclusion:

- Date of admission between May 1, 2017, and September 30, 2017.
- Patients younger than 2 years old.
- Acute community-acquired bronchiolitis as main diagnosis.
- Case discharge form completed (closing stage of the online registry).

Despite multiple national and international attempts, there is currently no unified standard for homogeneously diagnosing acute bronchiolitis. For this study, the criterion of the treating physician was the diagnosis of acute bronchiolitis.

The following variables were recorded from the selected cases: demographic data, comorbidities, severity scores (Pediatric Index of Mortality 3, PIM3)²⁷, ratio between pulse oximetry saturation and fraction of inspired oxygen (S/F ratio), validated respiratory failure scores for bronchiolitis in hospitalized infants (Liu²⁸ and Wang²⁹), initial and maximum respiratory support, and therapies used (bronchodilators, antibiotics, corticosteroids).

In the description and analysis of the therapy, we used the bronchodilator variable grouping all the drugs that have this effect as their main action (sal-

butamol, ipratropium bromide, magnesium sulphate and methylxanthines) and also each one independently. In the description and analysis of respiratory support, we classified into high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), and non-invasive ventilation (NIV) and, within this last one, continuous (CPAP) or bi-level positive airway pressure (BiPAP).

For the analysis of variability, the centers were grouped according to their geographical location (Atlantic: Uruguay and Argentina; Pacific: Chile, Ecuador, and Bolivia), type of health insurance system (public or private), and if they were academic medical centers in order to determine if there is a systematic difference among these groups, especially considering the ineffectiveness of the therapies.

The Anderson-Darling normality test was used to establish data distribution. The continuous variables were expressed as median (p25, p75) and the categorical ones as percentage and range or percentage and 95%CI. For the analysis, the Kruskal-Wallis test was used for the continuous variables, the Chi-squared test for the categorical ones, and the Bonferroni correction for the variability among centers. To increase the understanding and quantify the variability among centers, we used the coefficient of variation (CV). In our analysis, the CV is reported as percentage deviation of the average. Thus, the higher the CV, the greater the heterogeneity in the use of the described therapies. A $p < 0.05$ value was considered statistically significant.

Results

Characteristics of patients and participating centers

During the study period, 1,115 patients with acute respiratory failure were included in the registry, of which 467 cases were analyzed (figure 1). Only six patients were excluded due to insufficient data recording. 62.5% of the patients were male, aged 4 months (1.8-7.5), and with a 0.29% PIM3 score (0.17-0.57). The most common etiology identified was RSV (67%), and bacterial co-infection was suspected in 30%. The overall cohort had hypoxemia at admission classified as mild to moderate according to the FiO₂, and respiratory failure scores were in the moderate range. Table 1 shows the characteristics of the whole cohort and analysis of participating centers.

60% of the participating centers were in the Atlantic region, 25% were academic centers, and 50% were public health centers. Out of the patients included, 68% were from the Atlantic region, 32% from academic centers, and 53.3% from public centers.

Respiratory support

The most used maximum respiratory support was HFNC accounting for 46.6% (4.4 to 88%), followed by NIV with 26.1% (0 to 93%), and IMV 16.9% (0 to 100%). 35 patients used nasal cannula as maximum respiratory support. In the analysis by geographical area, in the Atlantic region the HFNC was mostly used (66.4%), while in the Pacific region there was greater use of NIV (71.5%). These same differences in maximum respiratory support frequency were observed when comparing public and private centers and between academic and non-academic ones (figure 2). When comparing the maximum support by center, there were statistically significant differences in its use (Supplementary figure 1, available online). Figure 2 shows the coefficient of variation of the maximum respiratory support mode, highlighting an important variation in the use of all of them, especially in NIV.

Out of the patients who needed IMV, 8.9% (7/79) of them required tracheal intubation before PICU admission. IMV was the first modality of support used at admission in 20% (16/79) of the patients, and in 70.1% (56/79) IMV was used after failure of other support.

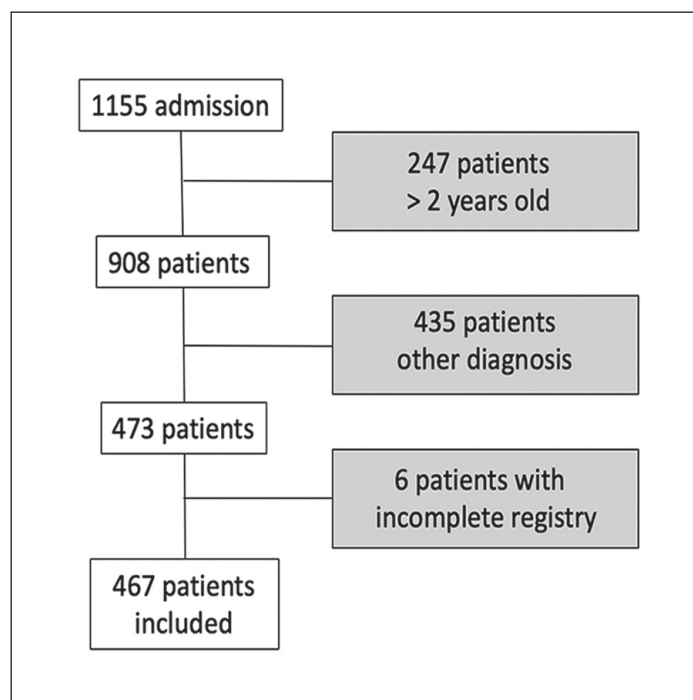


Figure 1. Patient flow of included cases in the analysis according to inclusion/exclusion criteria.

Table 1. Clinical and demographic characteristics of patients and descriptive analysis of the included centers

	Patient Analysis (n = 467)	Center Analysis (n = 20)
	Median (p25,p75)	Median (p25,p75)
Age (mo)	4 (1.8;7.5)	3.6 (2.9;3.9)
Weight (kg)	6.4 (4.6;8.5)	6.1 (5.76;7.1)
Male (%)	62 (IC95% 58;66)	62 (56;67)
Comorbidities (%)	33 (IC95% 29;37)	28 (10;37)
RSV (%)	67 (IC95% 62;61)	69.3 (53.2;81.4)
S/F ratio	316 (220;357)	332 (242;339)
LIU Score	5 (3;7)	6 (5;7)
WANG Score	4 (2;6)	5 (3;6)
PIM 3 (% _c)	0.29 (0.17;0.57)	0.26 (0.18;0.42)
VM duration (hours)	86.1 (66.2;134.4)	NA
PICU LOS (days)	4.5 (3.8;7.9)	4.7 (3.9;6.1)

The first column shows the analysis of all the patients. The second column compares the median between centers. RSV: respiratory syncytial virus; p: percentile; PIM 3: Pediatric Index of Mortality 3; LIU Score, WANG Score: clinical severity scales of acute respiratory failure. NA: non-available; IC95%: 95% confidence interval.

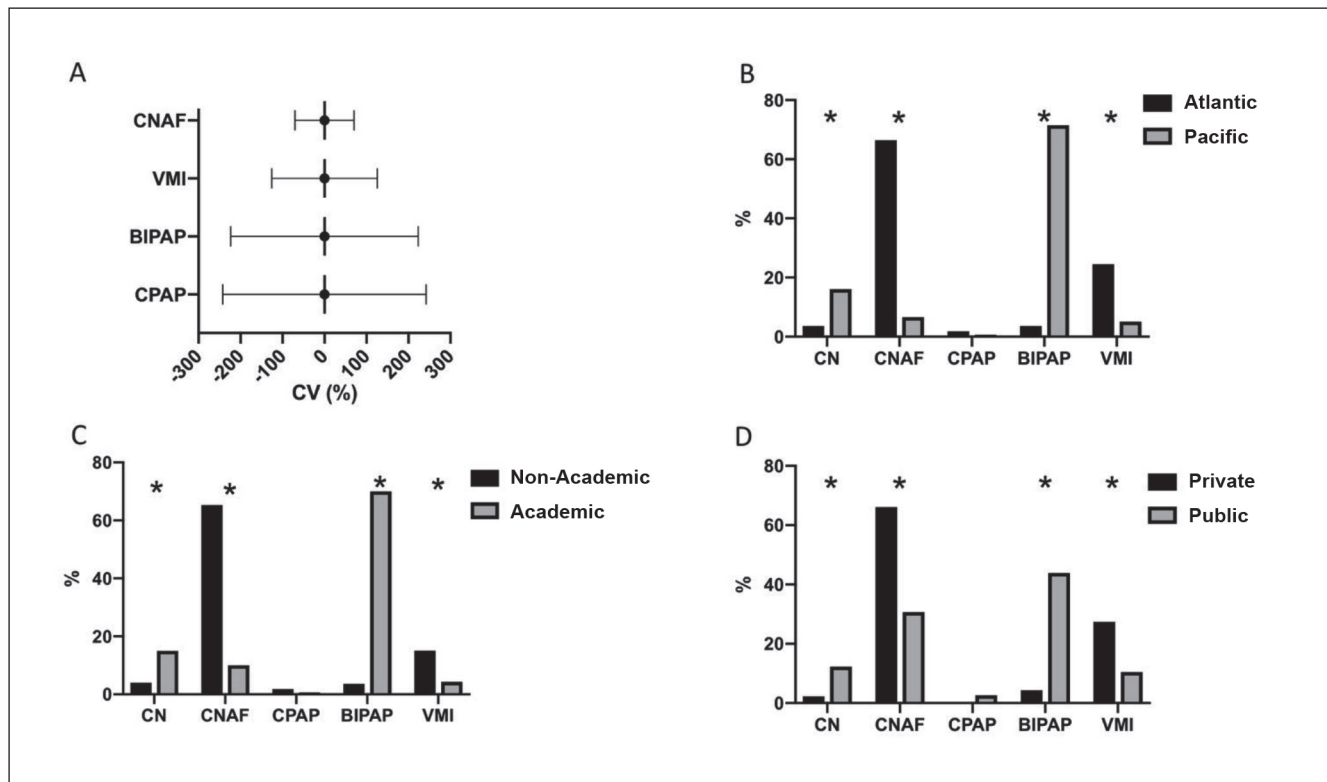


Figure 2. Maximal respiratory support in the whole cohort of community acquired bronchiolitis of LARed Network. **A.** Variation coefficient (CV) between participant centers; **B.** Atlantic vs Pacific; **C.** Non-Academic vs Academic; **D.** Private vs Public funding. * $p < 0.05$. CN: nasal cannula; CNAF: high flow nasal cannula; CPAP: continuous positive airway pressure; BIPAP: bilevel intermittent positive airway pressure; VMI: invasive mechanical ventilation.

Regarding the ineffectiveness of non-invasive modalities, NIV was less effective in the Atlantic region than in the Pacific one (50% vs 1%, $p < 0.01$), with no difference with HFNC.

When comparing public and private centers and academic and non-academic ones, there were no significant differences in NIV failure (50% vs 2.9% and 50 vs 2 % respectively) and HFNC failure (20% vs 18% and 19% vs 22% respectively).

Complementary therapies

Bronchodilators were used in 78.6% of cases. When comparing regions, bronchodilators were more frequently used in the Atlantic region than in the Pacific one (88.1% vs 57.3%, $p < 0.05$) (figure 3).

The overall use of nebulized epinephrine (L-form or racemic) was 23.2% and hypertonic saline was 23%. Both therapies were more frequently used in the Pacific region, in academic centers and in public institutions (figure 3, Supplementary figure 2, available online).

Antibiotics were used in 55.9% (range between 30% and 100%) and corticosteroids in 30% (range between 0% and 100%) of cases, with no differences

between the subgroups analyzed (figure 3). However, in the analysis of variability among the participating centers, there was a significant difference in corticosteroid use ranging from 0 to 100% ($p < 0.05$) (Supplementary figure 2).

The frequency of bronchodilators use was 89.9% of salbutamol, 13.4% of ipratropium bromide, and 7.3% of methylxanthines. The use of salbutamol and methylxanthines was more frequent in the Atlantic region, while the use of ipratropium bromide and magnesium sulfate was higher in the Pacific one (figure 4).

In the analysis of variability among the participating centers, we found significant differences in the use of salbutamol, ipratropium bromide, and methylxanthines (Supplementary figure 3). Figure 4 shows the CV of the complementary therapies, highlighting that, in five out of the nine therapies, the CV was higher than 100%.

Regarding clinical outcomes, the stay in PICU was 4.5 days (3.8-7.9 days) with significant differences between the participating centers. In this cohort, only one patient died of sepsis and acute respiratory distress syndrome.

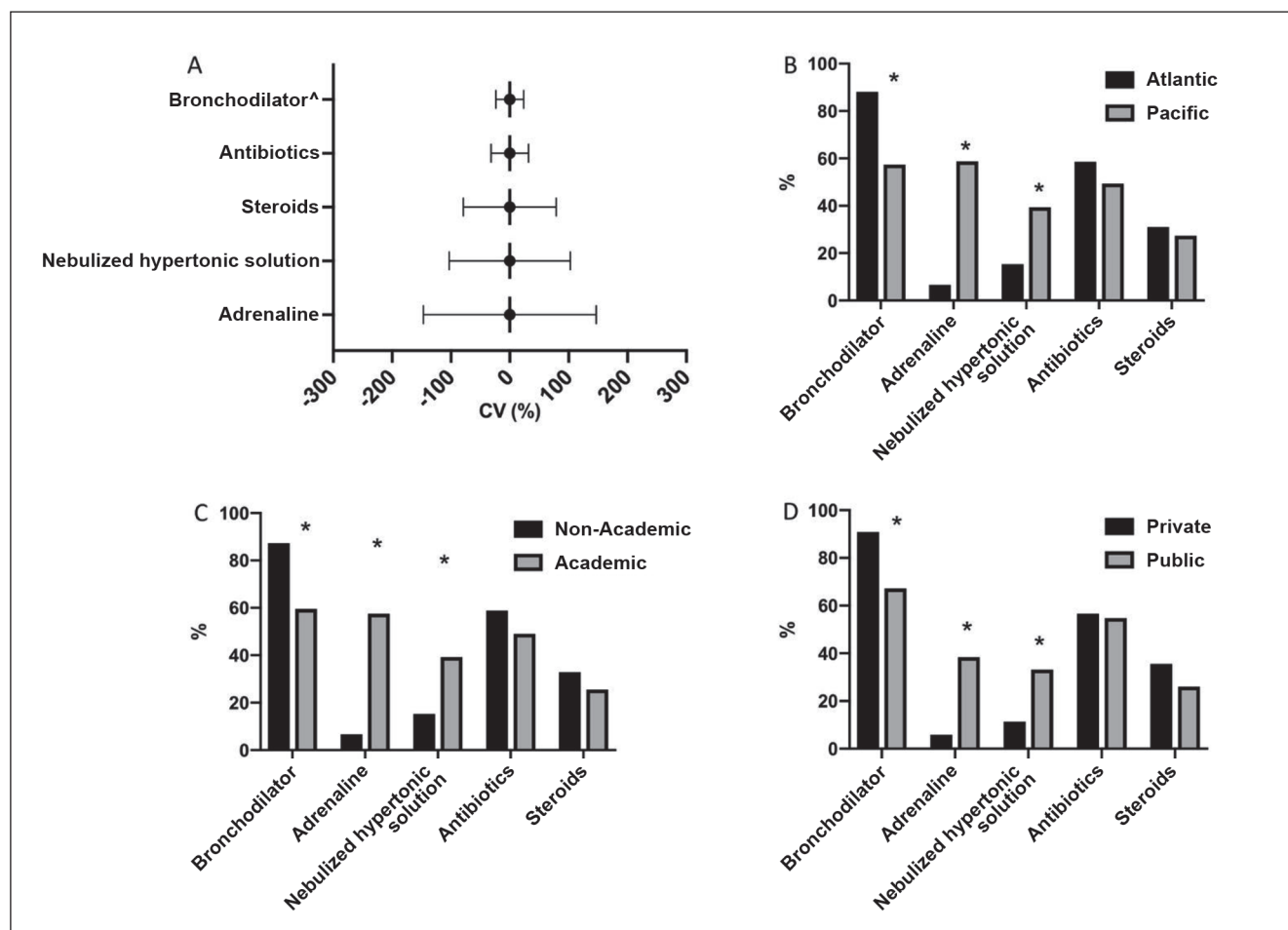


Figure 3. Pharmacological therapy used in the cohort. **A.** Coefficient of variation (CV) of participating centers; **B.** Atlantic vs Pacific; **C.** Non-Academic vs Academic; **D.** Private vs Public funding. * $p < 0.05$. [^]Bronchodilator refers to any therapy for bronchodilation, including Salbutamol/albuterol, Ipratropium Bromide, Aminophylline and Magnesium Sulphate.

Discussion

In this study, we used the LARed registry to describe the therapeutic approach of patients with acute bronchiolitis in Latin America. The main result of our study is that there is a wide variability in respiratory support modalities and pharmacological therapies which cannot be explained due to regional demographic differences or the variability in severity at admission to PICU.

This cohort of bronchiolitis is representative of Latin America, but is frequently observed worldwide: young infants, one-third of them with comorbidities, with moderate respiratory distress, and without severe hypoxia^{11,22,30}. The most frequent etiology identified was RSV and the PICU stay lasted less than one week. It is in this scenario that variability emerges as a significant problem for health systems and also for over- and under-treated children and their families^{30,31}.

Regarding respiratory support, non-invasive mo-

dalities such as HFNC and NIV were more frequently used than IMV. There was a notable difference between the Atlantic group, where the HFNC use was prevalent, versus the Pacific group, where the BIPAP use predominated. The minimal use of CPAP in Latin America is noteworthy, since it is a therapy widely recommended and used in other regions of the world and which has proved to be even better in more severe patients^{32,33}. Although there is no a categorical description of the superiority of a respiratory support modality, we believe that regional differences when choosing it can be explained by the familiarity and knowledge of those most frequently used³³⁻³⁹.

In our work, we detected a wide use of non-guideline based therapies¹⁴⁻¹⁶, highlighting the use of bronchodilators such as salbutamol, nebulized epinephrine, ipratropium bromide, and methylxanthines, with a wide range of variability between centers and categorization groups. Within the subgroups analyzed, the regional difference between bronchodilator groups is

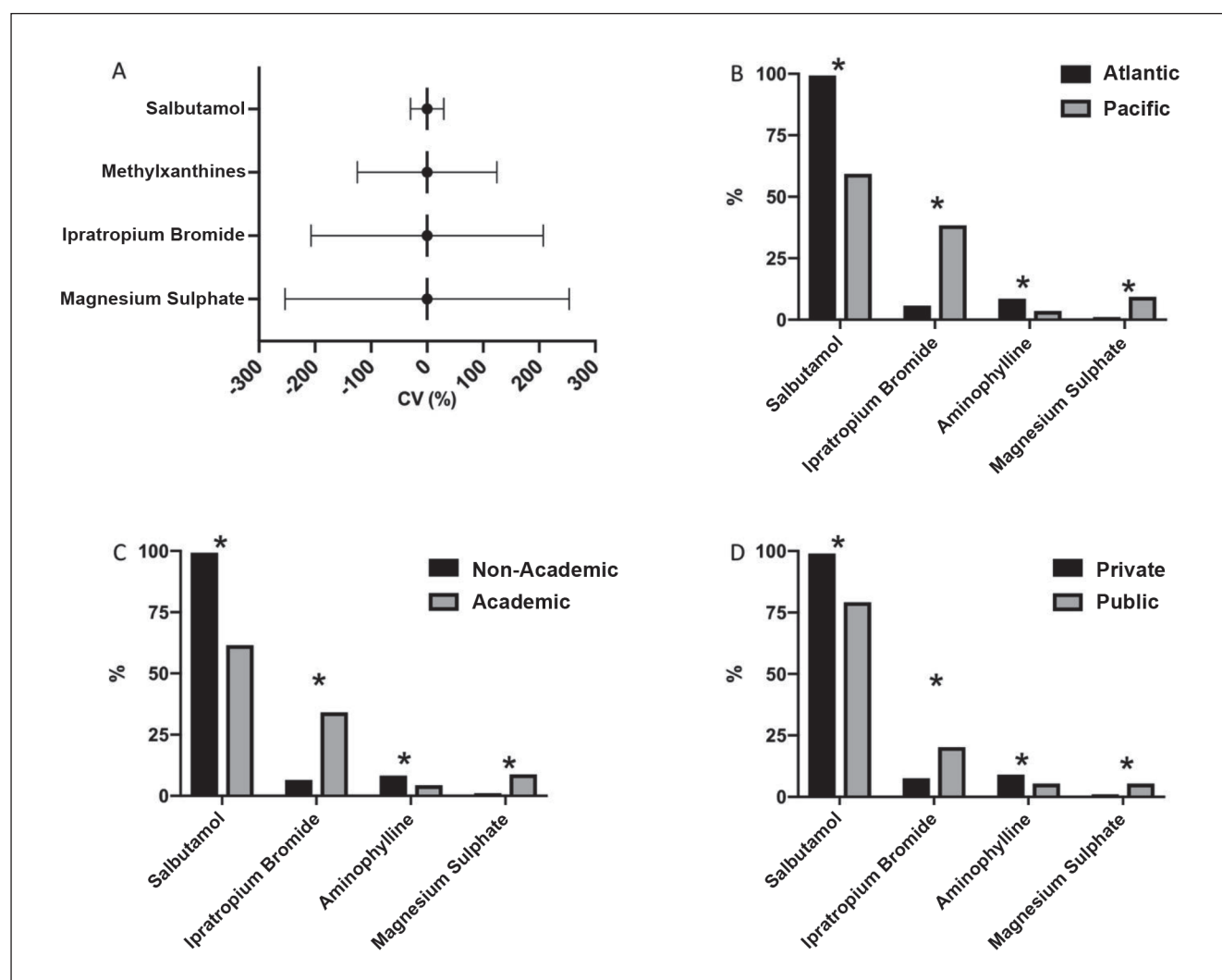


Figure 4. Bronchodilator therapy used in patients included in the study. **A.** Coefficient of variation (CV) of participating centers; **B.** Atlantic vs Pacific; **C.** Non-Academic vs Academic; **D.** Private vs Public funding. * $p < 0.05$.

very notable. In the Atlantic region, they preferentially used salbutamol and methylxanthines; extremely different from what was observed in the Pacific region, where racemic epinephrine, ipratropium bromide, and nebulized hypertonic saline were commonly used. The CV allows us to appreciate that there were therapies with a use variability higher than 200%.

One point to bear in mind is that it was not possible to specifically characterize the severity of each case analyzed and it is not possible to standardize the appropriate therapy, but even in a heterogeneous group of cases, such as this cohort, the use of pharmacological therapy should be exceptional.

The high use of antibiotics in 2/3 of the patients is striking, despite the fact that superinfection was suspected in 30% of the patients at admission and the use of corticosteroids in 1/3 of the children studied

(therapies known as useless), showing no differences between the groups analyzed. This could be due to the analysis of a selected population with bronchiolitis and, given the more severe condition of the patient in the PICU, interventions (justified or not) aimed at preventing further worsening are carried out, however, they could increase the vital risk. This care variability is a phenomenon that impacts the direct patient care not only in Latin America but has also been observed in cohorts in North America and Europe^{23,30,31,40}.

The overuse of treatments represents a major problem in the quality of medical care and is one of the main causes of wasting financial resources in health care⁴⁰. Based on the available evidence, this is defined as care that has no benefit and, sometimes, may even be counterproductive. The optimal management of acute bronchiolitis is still under debate and, although

existing guidelines do not provide specific therapies for those patients admitted to the PICU, their application should allow us to reduce this wide therapeutic variability with no scientific basis^{17,41}. Management and quality initiatives have been implemented in recent years, aimed at reducing waste of financial resources in bronchiolitis by decreasing the overtreatment of infants with this condition⁴²⁻⁴⁴.

This study has some limitations, such as the diagnosis of acute bronchiolitis was made according to the clinical evaluation of the physician who admitted the patient to the PICU, which could lead to a case selection bias. This is one of the frequent limitations of bronchiolitis studies worldwide, without distinction between geographical areas or the socio-economic development of the countries^{22,23,30,41}.

This variability was also influenced by the geographic/political extent of the cohort, with large differences in climate, health care system, as well as available resources. The participating centers could have different degrees of admission complexity that was not a recorded variable, which could influence the analysis of maximum respiratory support and therapies used.

Finally, we must emphasize that the participating centers are not necessarily representative samples of their respective countries, and there is an inequality in the volume of patients that participated in the different centers and countries. For this reason, we consider irrelevant to carry out independent analyses by country.

Despite these limitations, we believe it is important to report that acute bronchiolitis is the main cause of admission to PICU due to acute respiratory failure in infants in Latin America. There is wide variability in respiratory support and therapies administered, which cannot be explained due to the differences between populations or the severity of the disease. This variability should promote collaborative studies and promote educational activities, which will help to reduce the gap between scientific evidence and care practice, therefore, avoiding the inappropriate use of therapies.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients

and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Funding

Fondo Nacional de Ciencia y Tecnología, Gobierno de Chile, FONDECYT# 11160463 to F.D. for on-line tools and registry development; FONDECYT# 1160631 to P.C. for data analyses and web-based environment construction.

Acknowledgement

We thank all the participants of LARed Network and their affiliated institutions that made possible this manuscript: Hospital Regional de Antofagasta, Chile: Pietro Pietroboni Fuster; Hospital General de Medellín, Colombia: Yurika López-Alarcón, María lucía Cataño-Jaramillo, Alejandro Marín-Agudelo, Daniel Arango-Soto; Hospital Dr. Guillermo Rawson, Argentina: Javier Ponce, Lellis Figueroa; Médica Uruguaya, Uruguay: Martha Carbonell; Sanatorio Semm Mautone, Uruguay: Karina Etulain, Nora Mouta, María Parada; Hospital Evangélico, Uruguay: Loredana Matray, Cecilia Mislej, Eugenia Amaya; Corporación Médica Canelones, Uruguay: Carolina Talasimov, María José Caggiano; Hospital Central Reconquista, Argentina: Evelin Cidral Muniz, Alejandro Mansur; Hospital de Especialidades Materno Infantil- Caja Nacional de Salud, Bolivia: Juan Antonio Bravo Serrano; Hospital Regional de Salto Uruguay: Alejandro Franco, Luis E. Pedrozo; Hospital Regional San Juan de Dios Bolivia: Nils Casson Rodríguez, Estela Perales; Corporación Médica Paysandú Uruguay: Luis Martínez Arroyo, Silvia Dubra; Complejo Asistencial Hospital Dr. Sótero del Río, Santiago, Chile: Loreto Céspedes; Complejo Asistencial Dr. Víctor Ríos Ruíz, Chile: Ivette Padilla Maldonado, Juan Sepúlveda, Diego Aránguiz Quintanilla; Círculo Católico, Uruguay: Ema Benech, Mónica Carro; Hospital Central de las Fuerzas Armadas, Uruguay: Javier Martínez, Krystel Cantirán, Cristina Courtie; Hospital Regional de Tacuarembó, Uruguay: Soledad Menta, Laura Madrugá; Hospital Policial, Uruguay: Raúl Navatta, Andrea Iroa; CAMDEL Minas, Uruguay: Luis Castro, Argelia Cantera, Patricia Clavijo; Clínica Infantil Colsubsidio Colombia: Rosalba Pardo Carrero; Hospital Inglés Ecuador: Jaime Farez, Isabel Chanatasig, Romer Guachichulca.

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