

## Costs of Surfactant Therapy for Bronchiolitis in Critically Ill Infants

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### Abstract

**Background:** The use of Surfactant for mechanically ventilated infants with bronchiolitis decreased the duration of stay in the intensive care unit and had favorable effects on oxygenation and carbon dioxide removal. This study aimed to estimate the expected costs of surfactant therapy for bronchiolitis in critically ill infants in Colombia.

**Methods:** A decision tree model with four outcomes (hospitalization, mechanical ventilation with acute complications, mechanical ventilation without acute complications, and death) was used to estimate the expected cost per patient of surfactant therapy (ST) versus control or non-surfactant therapy (no-ST) for the treatment of infants with a diagnosis of bronchiolitis, requiring mechanical ventilation. The costs of each outcome were estimated from medical invoices of 193 infants with a diagnosis of bronchiolitis. To estimate the probabilities we conduct a systematic literature review of observational studies up to July 2020.

**Results:** The costs correspond to an expected cost per patient for the scenario with ST was US\$ 247 (CI 95% US\$ 243 - 251) and for the scenario without ST US\$ 253 (CI 95% 250 - 256), with a saving per patient of US\$ 6 (p = 0.02). When the drug cost of Surfactant was higher than US\$257 per patient the expected cost of ST was higher than no ST

**Conclusion:** ST was cost-saving in emergency settings for treating infants with severe bronchiolitis requiring mechanical ventilation. This evidence can be used by decision-makers in our country to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

**Keywords:** Surfactant; Colombia; Acute Bronchiolitis

### Introduction

Bronchiolitis is a viral disease characterized by respiratory distress, typically affecting infants under 12 months of age. More than a third of all infants develop bronchiolitis, of whom 3% of the patients are admitted to hospital in developed countries [1]. This hospitalization rate increase between 12 - 15% in developing countries especially due to problems and barriers in access to health services especially due to untimely care generated by barriers to initial access to health services [2,3]. The case-fatality rate by severe bronchiolitis in the first two years of life is usually 0.5% to 1.5% in high-income countries, but increase to 1.74% in Latin-American [4]. In Colombia, we estimate 260,873 years of life (CI 95% 208,180-347,023) were lost due to RSV bronchiolitis in Colombian children under two years [5].

This high morbidity is associated with increasing costs over the past several decades. In the United States the reported mean annual healthcare utilization for bronchiolitis per 1000 infants under 6 months of age is 17 hospitalizations, 55 ED visits and 132 unplanned office visits [6], with a total annual costs for bronchiolitis-related hospitalizations of \$543 million [7]. In Colombia, we reported high costs are due especially to inappropriate use of drugs and medical test [8,9]. In this context, having cost-saving interventions can reduce fatalities and allow efficient resource allocation, in a scenario of very limited resources such as occurs in developing countries.

Bronchiolitis treatment's mainstay is supportive measures, such as adequate fluid intake, antipyretics, and oxygen supplement. The requiring of mechanical ventilation is associated with an absence of surfactant activity [10]. The pulmonary surfactant is a surface active lipoprotein (80% phospholipids) complex secreted by type II alveolar cells that reduce surface tension and prevent alveolar collapse [11]. Exist two types of surfactans available for clinical use: animal or synthetic surfactant. The use of exogenous surfactans in preterm infant with hyaline membrane disease is the standard management for this condition [12]. Exogen surfactant in mechanically ventilated infants decreased duration of stay in the intensive care unit and had favorable effects on oxygenation and carbon dioxide removal. The pooled mean duration of mechanical ventilation (hours) in the intervention groups was 63.04 lower in the three randomized clinical trials included in this review [13]. This effect can have a positive economic impact on health services, especially in developing countries. This study aimed to estimate the expected surfactant therapy costs for bronchiolitis in critically ill infants in Colombia.

### Methods

#### Study design

We compared the cost of two alternatives for the treatment of infants (0 to 60 months of age) in an intensive care unit (ICU) with a diagnosis of bronchiolitis, requiring mechanical ventilation:

- Surfactant therapy (ST): intratracheal administration of Surfactant.
- Control or non-surfactant therapy (no-ST): placebo, or no intervention or standard care (humidified oxygen or adrenaline nebulization, or both).

#### Time horizon

The time horizon defined was of an acute episode of severe bronchiolitis.

#### Economic model

A decision tree model was used to estimate the mean expected cost per patient of ST and no-ST (Figure 1). In the economic model, we defined the following outcomes according to the natural history of bronchiolitis: Patient no hospitalized with ambulatory treatment, hospitalized patient not critically ill, hospitalized patient requiring mechanical ventilation with acute complications, hospitalized patient requiring mechanical ventilation without acute complications, and death.

#### Intervention

Exogenous Surfactant (intratracheal administration of Surfactant) in infants less than two years old requiring mechanical ventilation. The information on effectiveness was extracted from a systematic review of three RCTs [13]. In this study, the duration of the intensive care unit (ICU) stay was less in the ST than the control group: MD - 3.31, 95% CI - 6.38 - 0.25 days. Serious adverse effects were not reported in these studies. Respect to the drug administration in these trials:

The Luchetti 1998 included infants on mechanical ventilation for 24 hours without significant improvement of their clinical status (uncorrected congenital heart disease and neuromuscular diseases were excluded by two studies). In this study, porcine surfactant (Curosurf) 50 mg/kg was administered in two to three doses through an endotracheal tube [14].

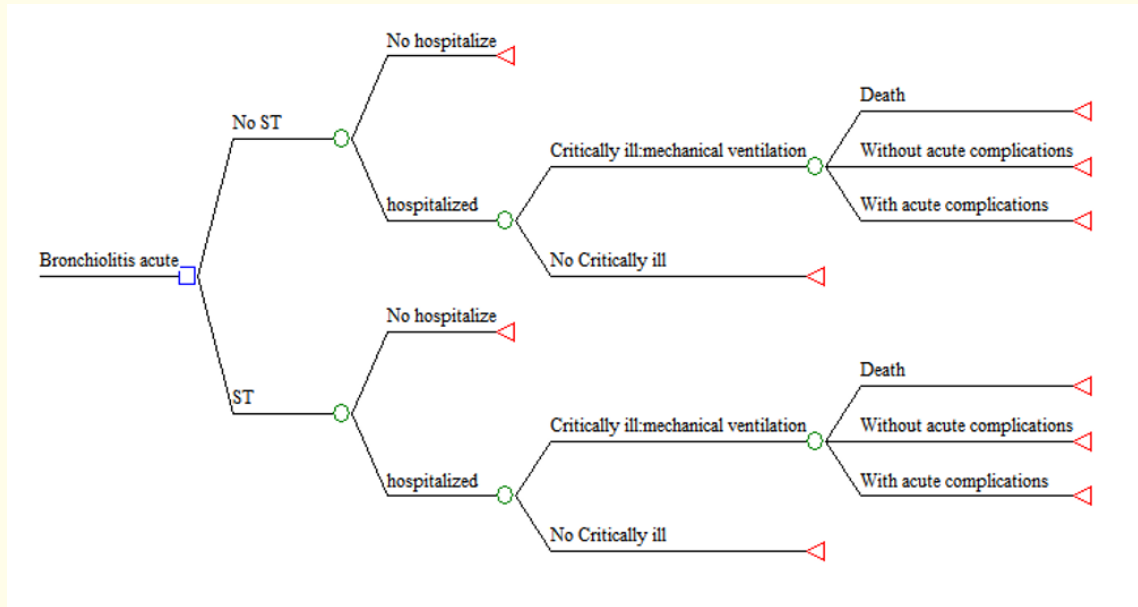


Figure 1: Decision Tree Model.

Luchetti 2002 included infants who had mechanical ventilation for at least 12 hours without significant improvement (uncorrected congenital heart disease and neuromuscular diseases were excluded by two studies). In this study, porcine surfactant (Curosurf) 50 mg/kg was administered in two aliquots over about five minutes, through an endotracheal tube [15].

The Tibby 2000 study enrolled infants who were ventilated for less than 24 hours with an oxygenation index above five and a ventilation index above 2 (study did not exclude children with chronic lung disease and prematurity history). In this study bovine surfactant (Survanta) was administered in two doses (100 mg/kg), 24 hours apart, through an endotracheal tube [11].

**Cost analysis**

The costs of each outcome were estimated directly from medical invoices, and electronic medical records of 193 infants admitted in tertiary centers in Rionegro, Colombia, with a diagnosis of bronchiolitis. This cost and clinical characteristics of these patients were published previously [8,16]. Brief, the direct costs considered in the analysis include medical consultation at the emergency room, specialist referrals, chest physiotherapy, diagnosis support (laboratory, electrocardiogram, x-ray, etc.), medication (oxygen, nebulization, antibiotics, corticosteroids, bronchodilators, etc.), medical devices, hotel services in the intensive care unit, and hotel services in the general medical ward. All treatment costs include the administration and preparation costs covered by the treating organization. All adverse events were assumed to be fully reversible, thus not causing any additional costs to the hospital district. To avoid data errors during medical record abstraction, we used software (Excel MS®) with automatic calculation functions and error alerts and a review of outliers by the research team. We used US dollars (currency rate: US\$ 1.00 = COP\$ 3,000) [17] to express all costs in the study. To evaluate the indirect costs, the human capital method was used, assuming everyone receives an income of at least a legal minimum wage for formal or informal work. The cost-opportunity of the productivity loss at the workplace and the caregiver was assessed based on the minimum wage with-

out including transportation assistance (US\$ 229.81 per month). The legal minimum wage approved by the government was taken as a reference and not an average or median wage thereof, given that in Colombia over 75% of the population has this value as their income [18]. Because all patients with acute asthma episodes included in this study were children, we assumed that at least one family member accompanied the patient permanently during hospitalization. Pediatric hospitals in the country usually allow only one companion per patient in the hospital. The cost associated with transportation and food (does not include a stay), was assumed to correspond to 50% of minimum wage per day.

**Probabilities**

To estimate the probabilities of the decision tree model (probability of hospitalization, probability of mechanical ventilation with acute complications, probability of mechanical ventilation without acute complications, and death) we conduct a systematic literature review of observational studies up to July 2020 Colombian population [18]. To identify potentially relevant studies, we searched computerized databases (MEDLINE, CENTRAL, LILACS, and CINAHL) using the following search strategy: (Colombia) AND (bronchiolitis) AND (children). No language restrictions were applied. The computerized search yielded 60 citations, and a total of 10 studies were examined in full text for possible inclusion. Finally, 5 studies were included to extract the information to the economic model (19 - 23) table 1 and 2.

Model Input	Base Case Value	SA Range For One-Way Sensitivity Analyses	Source
Probability			
Hospitalization	0,259	0,014-0,411	(19)
PICU-mechanical ventilation	0,079	0,061-0,182	(20)
Mortality, given PICU admission	0,009	0,009-0,067	(21)
Acute complications, given PICU admission	0,153	0,150-0,536	(22, 23)

**Table 1:** Probabilities Used in the Model.

**Data analysis**

A decision tree model was used to estimate the mean expected cost per patient of ST and no-ST. The validity of the estimates was evaluated, first by a tornado graph and the permissible limit values to determine the variables with the most significant influence on the sensitivity analysis. Also, a probabilistic sensitivity analysis was made using the Monte Carlo technique with a simulation of a hypothetical cohort of 10 000 patients. Each parameter varied randomly according to certain distributions (beta distribution in the case of probabilities, and gamma distribution in the case of costs) according to the recommendations of Briggs; to generate 95% confidence intervals (95% CI). The Tree age 3.5 statistical packages was used in all analyses.

**Results**

**Base-case results**

The expected cost per patient for the scenario with ST was U\$ 247 (CI 95% US\$ 243-251) and for the scenario without ST U\$ 253 (CI 95% 250-256), with a saving per patient of US\$ 6 (p = 0.02). This difference was due mainly to the lower cost of expected cost per patient in mechanical ventilation patients for the scenario with ST was U\$ 245 (CI 95% US\$ 232-259) and for the scenario without ST U\$ 267 (CI 95% 259 - 276), p = 0.006.

The broader changes in the expected values were seen with variations in the probability of hospitalization, followed by changes in the probability of ventilation, figure 2. In the one-way sensibility analysis, the expected cost of ST was always lower than no ST except in

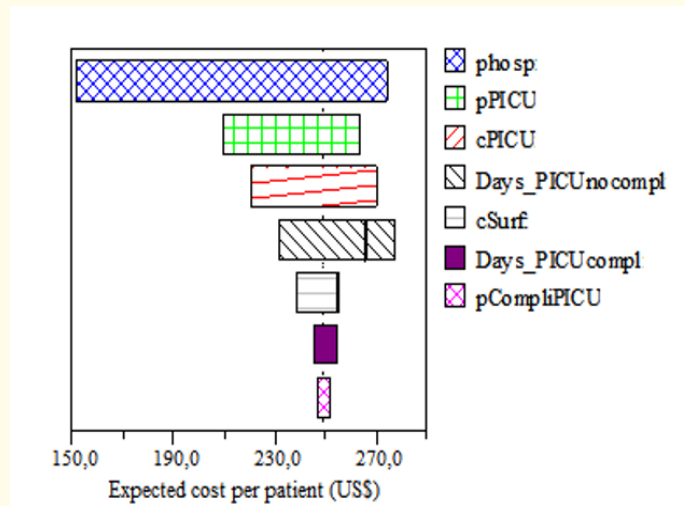
Model Input	Base Case Value	SA Range For One-Way Sensitivity Analyses	Distribution
Intervention cost			
ST per patient day	203	43-352	$\gamma$ (SD:197)
Hospitalization cost			
Daily cost in pediatric ward	48.82	47,64 50.00	$\gamma$ (SD:3,20)
Hospital length of stay (days)	5,8	4,00-6,01	$\gamma$ (SD:2,03)
PICU related cost			
Daily cost in PICU	327,35	326,26-328-43	$\gamma$ (SD:5,49)
Reduction in PICU length of stay (days) by ST	3.31	0.25-6.38	$\gamma$ (SD:1.8)
Emergency visit prior hospitalization cost			
Daily cost of emergency ward	12,83	12,19-13,46	$\gamma$ (SD:3,20)
Direct medical cost per patient-day			
Specialist referrals	10,67	10,31-11,01	$\gamma$ (SD:1,72)
Chest physiotherapy	5,15	4,90-5,39	$\gamma$ (SD:1,23)
Chest radiography	2,84	2,70-2,98	$\gamma$ (SD:0,73)
Others diagnostic imaging	0,01	0,0-0,022	$\gamma$ (SD:0,08)
Complete blood cell counts	1,12	1,05-1,17	$\gamma$ (SD:0,28)
RSV test	2,71	2,83-3,03	$\gamma$ (SD:2,72)
Other laboratory tests	4,40	4,23-4,47	$\gamma$ (SD:0,37)
Oxygen	1,37	1,28-1,45	$\gamma$ (SD:0,41)
Nebulization	16,23	1,28-1,45	$\gamma$ (SD:4,52)
LEV	1,10	1,07-1,13	$\gamma$ (SD:0,16)
Antibiotics systemics	1,21	1,11-1,30	$\gamma$ (SD:0,49)
Systemic o Inhaled Corticosteroids	0,08	0,0-0,90	$\gamma$ (SD:4,18)
Bronchodilators	0,04	0,03-0,04	$\gamma$ (SD:0,02)
Other drugs	0,65	0,60-0,68	$\gamma$ (SD:0,04)
Medical devices	10,24	9,71-10,76	$\gamma$ (SD:2,66)
Indirect cost patient-day	17,24	16.38-18,07	$\gamma$ (SD:4,30)

**Table 2:** Cost (US\$) Used in Base Case and Sensitivity Analyses.

three variables: drug cost of surfactant and PICU length of stay of a patient with acute complications. When the Surfactant’s drug cost was higher than U\$257 per patient, the expected cost of ST was more elevated than no ST, figure 3. When the PICU length of stay of a patient with acute complications was higher than 9.4 days, the expected cost of ST was higher than no ST.

### Discussion

Our study suggests that treatment with humidified oxygen or adrenaline nebulization without ST proved to be the most expensive therapy. Treatment with ST over four years was cost-saving thanks to the fewer cost of mechanical ventilation being observed with this regimen. Previous publications have shown that bronchiolitis has a relevant impact on healthcare resources consumption and related



**Figure 2:** Tornado Diagram.

*cSurf:* Cost of Surfactant Therapy Per Patient (US\$).

*pPICU:* Probability of PICU-Mechanical Ventilation.

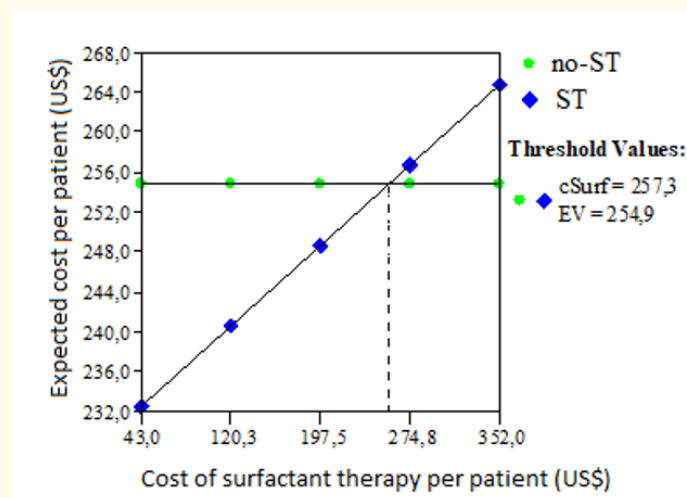
*cPICU:* Daily Cost in PICU (US\$).

*Days\_PICUnocompl:* PICU Length of Stay Per Patient, Patient Without Acute Complications (US\$).

*cSurf:* Cost of Surfactant Therapy Per Patient (US\$).

*Days\_PICUcompl:* PICU Length of Stay Per Patient, Patient with Acute Complications (US\$).

*pCompliPICU:* Probability of Acute Complications - PICU-Mechanical Ventilation.



**Figure 3:** Threshold Analysis of Cost of Surfactant Therapy.

*cSurf:* Cost of Surfactant Therapy Per Patient (US\$).

*EV:* Expected Cost Per Patient (US\$).

*Surfactant Therapy (ST).*

expenditures, especially in severe cases [5, 8, 20, 24]. All interventions that reduce the burden that this disease imposes on health systems is relevant, given its high frequency and morbidity [5].

Many treatments have been used in pediatric acute respiratory distress syndrome in children without even having therapy of choice [12]. Surfactant is the therapy with the highest level of expectations due to a positive effect in PICU length of stay, but still a few evidence in endpoints such as mortality. A recent study shows that the use of porcine Surfactant improves oxygenation, P/F ratio, and pH in a population of children with moderate or severe pediatric acute respiratory distress syndrome caused by multiple diseases [25]. In an infant with severe RSV infection, the administration in mechanically ventilated infants with acute respiratory failure due to RSV bronchiolitis improves gas exchange and respiratory and shortens the duration of mechanical ventilation, and PICU stay compared with control [13]. In patients with severe bronchiolitis, the duration of mechanical ventilation was no different in the surfactant group compared to the control group (mean difference (MD) -63.04 hours, 95% confidence interval (CI) -130.43 to 4.35), but there was a trend towards beneficial effects of Surfactant [13]. Otherwise, the ST is a safe treatment; in this systematic review, no adverse hemodynamic effects (no significant change in heart rate and blood pressure) were reported. In this sense, the ST would be a therapeutic option safe, with positive clinical effects in the PICU length of stay and the related health cost.

A relevant result was to find a drug cost of the ST per patient at which this therapy does not cost-saving. This threshold (US\$ 257) can be used as a reference for the control and regulation of prices in the country. This intervention has a positive effect, especially if the patient has a PICU length of stay less than 9 days. With a higher length of stay, the savings generated in the first days with PT have diluted the total cost. Having such information is relevant when transferring this evidence into clinical practice guidelines and optimizing the positive effects it can offer.

Our study has some limitations. We used retrospective data reported in a previously cost-effectiveness study, and this information does not exclude the possibility that medical invoices were incomplete or missing data. This study reported that several measures were employed to ensure data accuracy, including software with automatic calculation functions and error alerts and a review of outliers by the research team. Another limitation in the design was the assumption of complete adherence to this therapy, reducing ST's economic impact.

In conclusion, ST was cost-saving in emergency settings for treating infants with severe bronchiolitis requiring mechanical ventilation. This evidence can be used by decision-makers to improve clinical practice guidelines and be replicated to validate their results in other middle-income countries.

### Acknowledgements

None.

### Conflict of Interest

All authors declare that they do not have any conflict of interest in publishing this article.

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