





# *N*-acetilcisteína in acute respiratory distress syndrome: cost-effectiveness analysis for Colombia

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## ABSTRACT

**Introduction:** Acute Respiratory Distress Syndrome (ARDS) is a type of diffuse acute inflammatory lung injury usually of infectious origin that excessively increases oxidative stress, causes pulmonary tissue damage, negatively impacts the patient's condition, and can even lead to death. **Objective:** To evaluate the early use of intravenous *N*-acetilcisteína in adults with severe ARDS secondary to pneumonia of any etiology treated in intensive care units (ICUs), based on the number of avoided ICU days. **Materials and Methods:** Using a decision tree and data from Colombian health service providers, the ICU days that could be avoided by adding early intravenous *N*-acetilcisteína to the standard treatment of a patient with ARDS were calculated. Additionally, probabilistic sensitivity analysis was performed to assess the stability and robustness of the results obtained in the base scenario. **Results:** The average ICU stay was 8.38 days for standard management, compared to 6.84 days for standard management plus the addition of *N*-acetilcisteína. This difference implies an average reduction in healthcare costs of COP 4,067,125 per patient. Furthermore, the early incorporation of *N*-acetilcisteína into treatment was dominant, a result that remained constant in the sensitivity analysis. **Conclusion:** The early addition of *N*-acetilcisteína to ARDS treatment could result in a decrease in ICU days and savings in hospitalization costs.

**Keywords:** Adult respiratory distress syndrome; *acetilcisteína*; Critical care; Length of hospital stay; Cost-effectiveness evaluation.

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## N-acetilcisteína en el síndrome de dificultad respiratoria aguda: análisis de costo-efectividad para Colombia

### RESUMEN

**Introducción:** El síndrome de dificultad respiratoria agudo (SDRA) es un tipo de lesión pulmonar inflamatorio aguda difuso de origen, por lo general, infeccioso que incrementa en exceso el proceso de estrés oxidativo, causa daño tisular pulmonar y repercute negativamente en el estado del paciente e incluso puede provocarle la muerte.

**Objetivo:** Evaluar el uso temprano de N-acetilcisteína endovenosa en adultos con SDRA severo, secundario a neumonía de cualquier etiología, tratados en unidades de cuidado intensivo (UCI), en función de los días de estancia evitados.

**Materiales y métodos:** Mediante un árbol de decisión y datos provenientes de prestadores de servicios de salud colombianos, se calcularon los días de estancia en UCI que podrían evitarse al añadir N-acetilcisteína intravenosa temprana al tratamiento estándar de un paciente con SDRA. Además, se analizó la sensibilidad probabilística para evaluar la estabilidad y robustez de los resultados obtenidos en el escenario base.

**Resultados:** El tiempo promedio de estancia en la UCI fue de 8,38 días para el manejo integral, en comparación con 6,84 días para el manejo integral más la adición de N-acetilcisteína. Esta diferencia implica una reducción promedio en el costo de atención de COP4067 125 por paciente. Además, la incorporación temprana de N-acetilcisteína al tratamiento demostró ser dominante, resultado que se mantuvo constante en el análisis de sensibilidad.

**Conclusión:** La adición temprana de N-acetilcisteína al tratamiento del SDRA podría representar una disminución de los días de estancia en UCI y un ahorro en el costo de la atención hospitalaria.

**Palabras clave:** síndrome de dificultad respiratoria del adulto; acetilcisteína; cuidados críticos; tiempo de internación; evaluación de costo-efectividad.

## *N-acetilcisteína* na síndrome de dificuldade respiratória aguda: análise de custo-efetividade para a Colômbia.

### RESUMO

**Introdução:** A síndrome de dificuldade respiratória aguda (SDRA) é um tipo de lesão pulmonar inflamatória aguda difusa, geralmente de origem infecciosa, que aumenta excessivamente o processo de estresse oxidativo, causa dano tecidual pulmonar e repercute negativamente no estado do paciente, podendo até levar à morte.

**Objetivo:** Avaliar o uso precoce de N-acetilcisteína endovenosa em adultos com SDRA grave, secundário a pneumonia de qualquer etiologia, tratados em unidades de terapia intensiva (UTI), em termos de dias de internação evitados.

**Materiais e métodos:** Por meio de uma árvore de decisão e dados de prestadores de serviços de saúde colombianos, foram calculados os dias de permanência na UTI que poderiam ser evitados ao adicionar N-acetilcisteína intravenosa precoce ao tratamento padrão de um paciente com SDRA. Além disso, foi analisada a sensibilidade probabilística para avaliar a estabilidade e robustez dos resultados obtidos no cenário base.

**Resultados:** O tempo médio de permanência na UTI foi de 8,38 dias para o manejo integral, em comparação com 6,84 dias para o manejo integral mais a adição de N-acetilcisteína. Essa diferença implica uma redução média no custo de atendimento de COP 4.067.125 por paciente. Além disso, a incorporação precoce de N-acetilcisteína ao tratamento mostrou-se dominante, resultado que se manteve constante na análise de sensibilidade.

**Conclusão:** A adição precoce de N-acetilcisteína ao tratamento da SDRA poderia representar uma redução nos dias de permanência na UTI e uma economia nos custos do atendimento hospitalar.

**Palavras-chave:** síndrome de dificuldade respiratória do adulto; acetilcisteína; cuidados críticos; tempo de internação; avaliação de custo-efetividade.

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) “is a type of diffuse acute inflammatory lung injury, which leads to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue” (1). In the United States, around 190,000 cases and 74,000 deaths due to ARDS are estimated annually. Approximately 30.9% were severe cases requiring management in an intensive care unit (ICU) (2).

The multicenter LUNG SAFE study, which included data from 50 countries, reported that 10.4% of total ICU admissions were due to ARDS, of which 23.4% required mechanical ventilation, with an incidence of 0.42 cases/ bed ICU bed for more than four weeks (ARDS cases per number of available ICU beds), which was 0.31 for South America. Despite advances in support, increased severity of ARDS has been associated with prolonged ICU stays, more days of invasive mechanical ventilation, long hospital stays, and higher mortality rates, which were 35.3% in ICUs and 40% in hospitalization (3)

In a multicenter observational study based on 2016 data in Colombia, it was found that the mortality rate in ICUs for patients with severe ARDS was 37.5%; while hospital mortality reached 61.9%. The median duration of mechanical ventilation was 10 days (Q1: 8 days; Q3: 15 days).

Regarding ICU stay, the median was 20 days (Q1: 10 days; Q3: 75 days). The most identified risk factor in these patients was pneumonia, present in 48.8% of cases (4).

For a long time, ARDS has been recognized as a heterogeneous disease, not only because it varies among patients but also due to its different pathogenic factors and differences in the pulmonary damage generated, characterized by rapid progression and regional damage heterogeneity (5). Severe inflammation and destruction of the pulmonary barrier constitute the pathophysiological basis of ARDS, from which excessive oxidative stress activation occurs, with an increase in inflammatory mediators and cytokines, causing tissue damage (6,7). Among the most common causes of ARDS are pneumonia and sepsis. However, conditions such as aspiration, burns, and trauma, among others, can also lead to its development and generate a critical state in the patient (8).

Once ARDS develops, patients often require various treatments designed to address the pathophysiological process. These treatments may include corticosteroids, statins, surfactants, nitric oxide, antibiotics, or antivirals, depending on the associated conditions (9). Despite the continuous emergence of new drugs for ARDS, so far, none have proven to be beneficial in terms of reducing mortality in clinical trials. This is mainly due to

pulmonary barrier impairment, which reduces drug delivery efficiency and effectiveness (10).

Antioxidant agents like *N-acetilcisteína* (NAC), used as adjuncts in ARDS management, have been shown to significantly decrease oxidative damage by contributing to the restoration of the redox balance (11). In this scenario, NAC exerts a mucolytic action on lung secretions and provides *L-cisteína* residues necessary for glutathione synthesis, which would support its use in patients experiencing oxidative stress (12,13).

Some meta-analyses have provided evidence that early intravenous NAC administration in ARDS patients can significantly reduce the average duration of their ICU stay. In contrast to patients who did not receive NAC at the beginning of their treatment, studies conducted by Zhang et al. (14) and Lu et al. (15) showed a remarkable reduction in hospitalization time. Zhang et al. (14) reported that early introduction of NAC decreased ICU stay by an average of 4.56 days (mean difference: -4.56 days; 95% confidence interval (CI): -7.32 to -1.80;  $p = 0.001$ ;  $I^2 = 25\%$ ). Similarly, Lu et al. (15) observed an average reduction of 4.47 days in ICU stay for those patients who received NAC at the beginning of their treatment (mean difference: -4.47 days; 95% CI: -8.79 to -0.14;  $p = 0.04$ ;  $I^2 = 46\%$ ).

ARDS is generally a critical condition that leads to significant economic burdens on the health-care system worldwide. We aimed to analyze the cost-effectiveness of early intravenous NAC use in adults with severe ARDS, secondary to pneumonia of any etiology, as part of comprehensive treatment in the ICU, seeking potential benefits in terms of avoided ICU stay days, within the context of the Colombian healthcare system.

## MATERIALS AND METHODS

Using decision tree construction, we simulated the care of adult patients with severe ARDS admitted to the ICU, conducting a cost-effectiveness analysis that evaluated the early addition of intravenous NAC to the comprehensive treatment of these patients, from the perspective of the Colombian General System of Social Security in Health. The analyses were carried out using Excel program. The time horizon was determined by the duration of the hospital event, measured in days, which is why the discount rate was not applied. The studied population consisted of patients aged 18 years or older diagnosed with ARDS associated with bacterial, viral, or unspecified pneumonia, and hospitalized in the ICU.

The outcome evaluated was the number of ICU stay days avoided after the early use of NAC in the intrahospital care pathway, which was considered crucial by clinical experts (intensive care

medical specialists) consulted by the research group. For this purpose, initially, a systematic search for information was conducted until April 20, 2022, in the main databases, including Medline, Embase, Cochrane Systematic Reviews, Cochrane Clinical Trials, LILACS, and ClinicalTrials.gov. Search strategies focused on *Medical Subject Headings* (MeSH), such as *Respiratory Distress Syndrome, Adult, ARDS, N-acetylcysteine, and acetylcysteine*, applying specific filters for *clinical trial, controlled clinical trial, systematic review, and meta-analysis*, without restriction by date or language. This search resulted in the identification of two systematic reviews with meta-analyses published in 2017 (14) and 2019 (15). These provided relevant data on the duration of ICU stay for ARDS patients treated with NAC, compared to those who received placebo.

The economic evaluation was based on the information from the study by Lu et al. (15), selected for being the most updated for including the highest number of studies in its analyses, and for adequately presenting the assessment of the quality of the included studies. Additionally, the study properly organized clinical trials published before the coronavirus pandemic.

Direct healthcare costs were obtained using the top-down costing technique (*macro costing*), which involves starting from general data with specific characteristics to obtain specific data

according to expectations. The costing method chosen allows for variations in the cost of care to be considered, mitigating the risk of overestimating the value of the event, and allows for a representative value, as most costs are incurred for care within the hospital setting, which itself does not have a standard value for the same event, and can vary from patient to patient, decreasing or increasing its value depending on the particular case.

To calculate the macro costs, a database provided by a Colombian insurance company was used. The information covers from 2017 to 2019, with an annual average of 2,326,503 users. Subsequently, a retrospective analysis of cases derived from administrative records was carried out. These are based on individual records of service provision and were compiled according to the sufficiency bases of the per capita payment unit, reported to the Ministry of Health and Social Protection from 2016 to 2018. To update the costs to present values, they were adjusted to the actual consumed value and recalibrated to 2021 prices using the Consumer Price Index in the healthcare sector.

Using data mining techniques, clinical events with characteristics similar to those of the study population were identified, specifically those with a diagnosis of ARDS associated with any type of pneumonia. Two different groups were

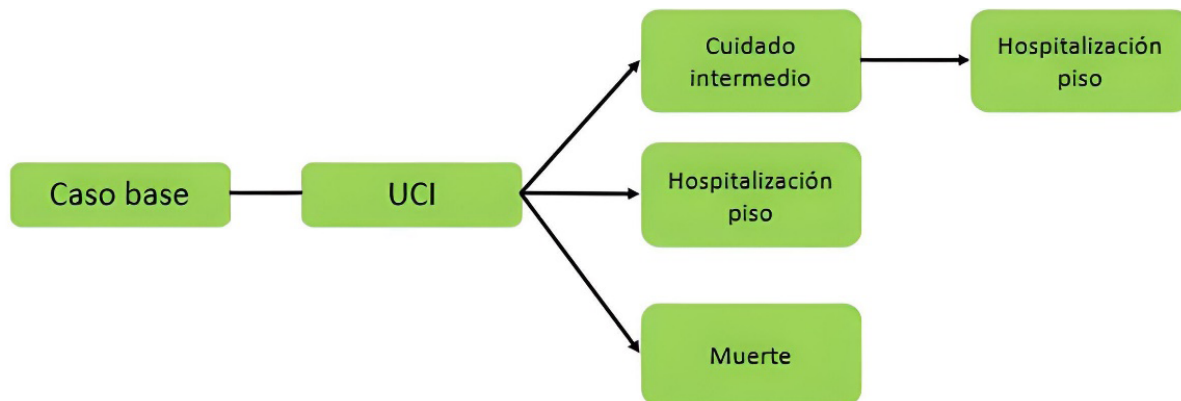
formed for analysis: one included patients who had received intravenous (NAC) as part of their comprehensive treatment in the ICU and another who had not. For each group, the average length of stay in the ICU was estimated, as well as the costs related to each hospital event. Events that did not meet validation criteria or had inconsistencies in the description of hospital services were excluded. Medication costs were estimated from the Integrated Drug Price System database for the last quarter of 2022.

The baseline scenario of this study represents a patient with severe ARDS derived from pneumonia, who is admitted to the ICU for ventilatory support and comprehensive care. During their ICU stay, the patient may show a positive progression, advancing to an intermediate care unit and subsequently to general hospitalization, or they

may be transferred directly to general hospitalization. In the case of an unfavorable outcome, the patient may not recover from the critical condition and may die. The duration of stay in each level of care depends on the patient's clinical evolution.

The study modeled two different scenarios: one including the use of NAC in the patient's treatment and another without its use. According to the reference literature, NAC administration is associated with an average reduction of 4.47 days in ICU length of stay, which corresponds to an 18.4% decrease in hospitalization time in this unit (15). Transition probabilities between different care states were based on real patient data from Colombian insurers, using averages and excluding other additional treatments in the model (Figure 1).

Figure 1. Decision Model



The current model assumes that: 1) there is clinical benefit from the early use of NAC when a patient is in the ICU, as there is an average reduction of 4.47 days of stay there (15), corresponding to an average decrease of 18.4%. 2) Admission to the ICU is due to the need for ventilatory support and is done early and timely. 3) The normal disease behavior (without the technology) is modeled based on the review of administrative data from cases evaluated as coinciding with the base case, extracted from different Colombian insurance sufficiency databases from 2016-2019, to show

results most similar to the Colombian context (before the COVID-19 pandemic). 4) Two groups of patients were established that generated the ARDS scenario, secondary to pneumonia regardless of its bacterial, viral, or nonspecific origin. 5) As an intervention, the administration of intravenous NAC was defined at a dose of 150 mg/kg every day for the first day and 50 mg/kg per day for the following three days, for 4 days (15), using an average weight of 70 kg as reference (Table 1).

**Table 1.** Model parameters

Parámetro	Value in base case	Sensitivity analysis range		Source
		Minimum	Maximum	
Days in ICU	8.38	6.70	10.05	Hospital care from Colombian insurer
Days in intermediate care	4.3	3.44	5.16	
Days in floor after intermediate care	10.03	8.02	12.04	
Days in floor after ICU	10.05	8.04	12.06	
Days in ICU who die	8.82	7.06	10.58	
Probability of transitioning from ICU to intermediate care (%)	31.98	25.58	38.38	
Probability of transitioning from ICU to floor (%)	26.51	21.21	31.81	
Probability of dying in ICU (%)	41.51	33.21	49.81	
Probability of reducing ICU stay days (%)	18.40	---	---	
Cost of NAC dose 10,500 mg first day (COP)	149,951	119,960	179,941	SISMED
Cost of NAC dose 10,500 mg for three days (COP)	349,886	279,909	419,863	
Average cost per day in ICU (COP)	2,861,456	2,289,165	3,433,747	Health services from Colombian insurer
Average cost per day in intermediate care (COP)	374,666	299,733	449,599	
Average cost per day in floor (COP)	204,501	163,601	245,401	

ICU: Intensive Care Unit; SISMED: Integrated System of Drug Prices.



This study does not adopt the threshold recommended by the World Health Organization and the *Instituto de Evaluación de Tecnologías de Salud*, which is less than three times the per capita gross domestic product, as this is only valid for outcomes such as years of life saved and quality-adjusted life years. In this case, we use the cost of an average day of stay as a reference for the proposed outcome analysis. Additionally, a probabilistic sensitivity analysis was conducted to assess the stability and robustness of the results found. The decision tree construction and statistical analyses were carried out using Microsoft Excel 2019.

## RESULTS

For a patient diagnosed with severe ARDS associated with any type of pneumonia, an average stay in the ICU of 8.38 days was estimated, compared to 6.84 days for those who, in addition to comprehensive treatment, received NAC as part of their management regimen. The cost of intravenous NAC was included according to the specified dose within the cost of the comprehensive ICU stay + NAC (Table 2).

Regarding the incremental related to effectiveness and cost between comprehensive management versus comprehensive management + NAC, it was estimated that the use of NAC reduces ICU hospitalization by 1.54 days (number of

**Table 2.** Cost breakdown

Technologies	Status	Cost (COP)
Comprehensive management	Stay in ICU	23,979,001
	Stay in intermediate care	515,218
	Stay on floor	1,200,799
	Total cost	25,695,018
Comprehensive management + NAC	Stay in ICU*	19,911,876
	Stay in intermediate care	515,218
	Stay on floor	1,200,799
	Total cost	21,627,893

ICU: Intensive Care Unit.

\* Includes the cost of *N-acetilcisteína* (NAC).

**Table 3.** Base case results

Technologies	Cost (COP)	Days of stay	Incremental cost	Incremental length of stay	ICER
Comprehensive management	25,695,018	8.38			
Comprehensive management + NAC	21,627,893	6.84	-4,067,125	-1.54	Dominant

ICER: Incremental Cost-Effectiveness Ratio.

ICU hospitalization days avoided) and that this reduction, in turn, represents a saving in costs associated with ICU stay of COP 4,067,125 per patient (Table 3).

## Sensitivity analysis

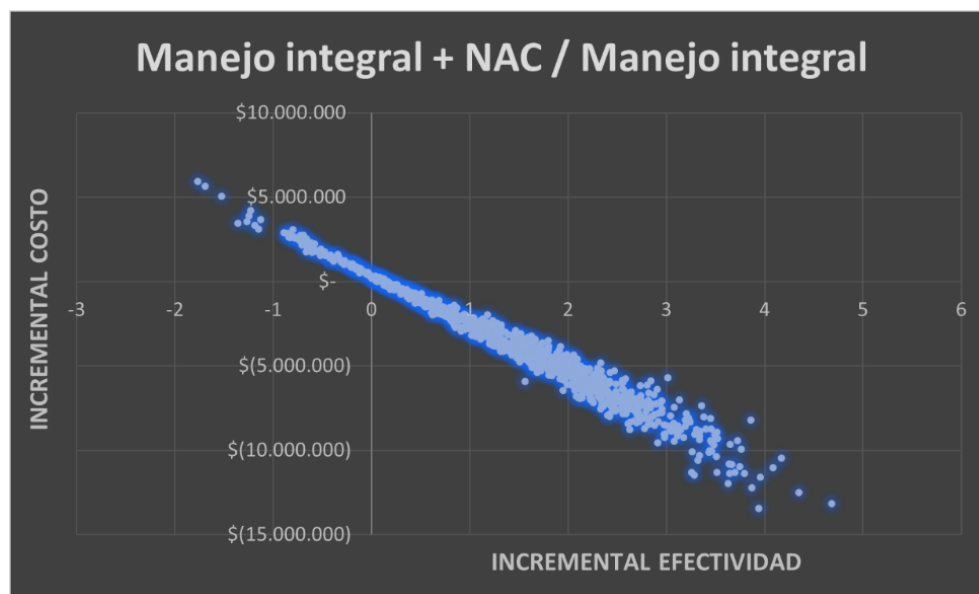
To evaluate the stability and robustness of the base case results, a probabilistic sensitivity analysis was conducted, in which a thousand iterations were run estimating the possible movements of the parameters used through various probability functions. Figure 2 presents the result of this analysis, in which the cost-effectiveness plane serves as a basis to illustrate the proportion of iterations found in each quadrant. Particularly, this analysis showed that 88.2% of the iterations would be dominant (as in the base case), 2.8% would be cost-effective, and 9% would be dominated.

As observed in Figure 2, the dispersion of the points is very close to a straight line, which is reasonable considering that the cost difference is a direct and immediate result of the incremental effectiveness (days avoided in ICU admission). In other words, as there is greater incremental effectiveness, the savings produced by the management scheme will be greater.

## DISCUSSION

NAC, known for its antioxidant and anti-inflammatory properties, has emerged as a potential therapeutic agent in the management of ARDS, a clinical

Figure 2. Sensitivity analysis



condition associated with high morbidity and mortality rates (16). In Colombia, a multicenter study published in 2019 highlighted the severity of this condition, revealing a mortality rate of 12% in ICUs during the first 96 hours, and 34% at 28 days. In addition, to a median duration of mechanical ventilation of 11 days and an average ICU stay of 14 days. This underscores the burden that ARDS imposes on both patients and health-care systems (17).

This economic analysis evaluates the impact of incorporating intravenous NAC into the comprehensive treatment of patients with ARDS secondary to pneumonia in the ICU. The results reveal that the inclusion of NAC reduces ICU stay by 1.54 days, resulting in a decrease of COP 4,067,125 in the overall cost of patient care. The analysis indicates that the use of NAC is a dominant strategy that offers better outcomes compared to standard treatment. Additionally, the probabilistic analysis showed that the strategy of adding intravenous NAC demonstrated dominance in approximately 88% of cases and generated cost-saving benefits in the final cost of care.

While the reviewed studies provided data on hospital stays, this analysis stands out for considering the variability in the management of patients with ARDS, which is influenced by the unique clinical context of each case. In this sense, the analysis is based on the average length of stay in

the ICU in Colombia and adjusts to local clinical practices and the application of this treatment approach.

The availability of ICU beds in the Colombian healthcare system is a constant challenge. According to data from the *Organización para la Cooperación y el Desarrollo Económicos*, in 2020, Colombia had an average of 10.3 ICU beds per 100,000 inhabitants, a figure lower than the average of 22 countries belonging to the same organization (12 beds per 100,000 inhabitants) and below Latin American countries such as Brazil, Uruguay, and Argentina (18). In this context, the findings of this study suggest that the use of NAC could improve hospital capacity by effectively increasing the number of available beds.

In the literature search, no data were found on cost-effectiveness evaluations addressing the use of NAC in the context of patients with ARDS secondary to pneumonia. This highlights the importance of the data obtained from our study, which may be considered for future analyses.

Among the limitations of this study is the lack of inclusion of data or models of patients with ARDS associated with COVID-19. This is because the study on which our information about the reduction in ICU length of stay is based was published in 2019, that is, before the onset of the pandemic. However, recent research, such as the syste-

matic review conducted by Sham et al., (19) indicates that the use of NAC could be beneficial for patients with COVID-19. The results of this review point to a decrease in mortality among patients treated with NAC compared to those who received placebo (RR: 0.65; 0.56-0.75;  $p < 0.0001$ ). Additionally, a significant reduction in C-reactive protein and D-dimer levels was observed, as well as a significant increase in oxygen saturation, reinforcing the evidence of the positive effect of NAC in the treatment of patients with COVID-19. Another limitation of the study is the lack of local data on the effectiveness of NAC for calculating the incremental cost-effectiveness ratio.

Despite the limitations of the study, this cost-effectiveness analysis provides evidence supporting the integration of NAC as part of the comprehensive treatment for patients with ARDS secondary to pneumonia in ICUs. The reduction in ICU stay and associated costs, along with the potential improvement in hospital capacity, suggest that NAC is a viable strategy to optimize the care of these patients and reduce expenses to the healthcare system.

## CONCLUSION

According to scientific evidence, the use of NAC in patients with acute respiratory diseases requiring ICU management with ventilatory support is associated with a reduction in ICU length of

stay. This decrease in hospitalization days leads to a reduction in the average cost of hospital care, which can exceed four million Colombian pesos. This saving occurs despite the additional cost of using NAC, which is considered a low-cost medication with an adequate safety profile.

From an economic perspective, the inclusion of NAC in the treatment of these patients remains advantageous, even when considering different scenarios and variations. The use of NAC not only generates significant savings for the healthcare system but also contributes to improving ICU bed turnover, thus optimizing the availability of critical resources.

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## CONFLICTS OF INTEREST

The authors declare that they have no known financial interests or personal relationships that could have appeared to influence the work reported in this document.

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