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Clinical Outcomes of Magnesium Sulphate and Aminophylline in Adult Acute Asthma: A Systematic Review and Network Meta-analysis

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Abstract
Magnesium sulfate ($MgSO_4$) and aminophylline are commonly used as adjunctive therapies in adults with acute asthma exacerbations who do not adequately respond to standard treatment. However, their comparative effectiveness remains uncertain. This network meta-analysis (NMA) aimed to evaluate the clinical outcomes of $MgSO_4$ and aminophylline in adults with acute asthma. A systematic review and meta-analysis were conducted following PRISMA guidelines, identifying articles from PubMed, SpringerLink, and Taylor & Francis. Random-effects models generated standardized mean differences (SMD) with 95% confidence intervals (CI). A league rank table was also generated to estimate the most effective agent in treating acute asthma. Overall heterogeneity was evaluated using the I^2 test.
The NMA demonstrated no statistically significant difference between $MgSO_4$ and aminophylline in improving FEV_1 (SMD = 0.68; 95% CI: −1.59 to 2.95; p = 0.5573). Ranking analysis suggested that, besides placebo, nebulized $MgSO_4$ had the highest probability of being the most effective intervention for FEV_1 improvement, although this finding did not reach statistical significance (nebulized $MgSO_4$: MD = 1.11; 95% CI: 0.20–3.38; p = 0.6641). Qualitative synthesis indicated that $MgSO_4$ was associated with improvements in PEFR. In addition, aminophylline showed a potential reduction in hospital admission rates, whereas results for $MgSO_4$ were inconsistent across studies.
$MgSO_4$ and aminophylline showed comparable effects on FEV_1 improvement in adults with acute asthma. $MgSO_4$ demonstrated favorable results in PEFR improvement, while aminophylline may offer potential benefits in reducing hospital admissions. Given the heterogeneity and limited sample sizes of available trials, further high-quality head-to-head studies are warranted to clarify their relative clinical effectiveness.

INTRODUCTION

Asthma is fundamentally characterized as a heterogeneous chronic inflammatory disease of the lower respiratory tract, manifesting through variable airflow limitation, bronchial hyperresponsiveness, and airway remodeling (Chen et al., 2025). As of 2021, the global prevalence of asthma was estimated at approximately 260.48 million individuals, representing an age-standardized prevalence rate (ASPR) of 3,340.1 per 100,000 population (Mao et al., 2025). While there has been a significant decline in age-standardized prevalence and mortality

rates globally between 1990 and 2021 — with a 38.7% reduction in ASPR — the absolute number of individuals affected continues to rise in many regions due to population growth, aging, and increasing urbanization (Wu, 2026).

Acute asthma exacerbations represent the most critical and potentially life-threatening phase of the disease (Al-Shamrani et al., 2019). In severe cases, physiological deterioration can lead to respiratory failure, profound respiratory acidosis, and cardiopulmonary arrest (Gayen et al., 2024). The primary objective in the acute management of asthma is the rapid reversal of airway obstruction and the mitigation of inflammation. Standard therapy, as outlined by the Global Initiative for Asthma (GINA), emphasizes the aggressive use of inhaled short-acting β_2-agonists (SABA) and systemic corticosteroids. For patients who do not achieve a sustained clinical response to initial standard therapy, adjuvant interventions become necessary (Dabbs et al., 2024). Secondary treatments such as intravenous magnesium sulfate ($MgSO_4$) and aminophylline are indicated in cases of severe or life-threatening exacerbations that are refractory to intensive SABA and steroid administration (Abu-Sultaneh et al., 2025).

Magnesium sulfate has established an indispensable role as an adjunctive therapy for severe asthma exacerbations that fail to respond adequately to conventional treatment (Mansour & Yousif, 2025). The clinical efficacy of intravenous $MgSO_4$ is supported by extensive systematic reviews and meta-analyses. Despite its proven benefits, the optimal route of administration for $MgSO_4$ remains a subject of ongoing research (Ambrożej et al., 2024).

On the other hand, aminophylline — a methylxanthine derivative consisting of theophylline and ethylenediamine — has a long history of use in the treatment of obstructive airway diseases (Aralihond et al., 2020). Despite these mechanistically attractive properties, the clinical application of aminophylline has significantly declined due to its narrow therapeutic index and the high frequency of associated adverse effects. Evidence regarding the clinical benefit of adding intravenous aminophylline to standard therapy remains inconsistent (Nair et al., 2012).

The decision to use $MgSO_4$ or aminophylline as a second-line therapy is often driven by institutional protocol or clinician preference rather than high-certainty comparative evidence, and significant gaps in the evidence base remain. This systematic review and meta-analysis therefore aimed to compare the efficacy of $MgSO_4$ and aminophylline for acute asthma in adults. The study offers both theoretical and practical benefits. Theoretically, it fills a critical gap in respiratory emergency medicine by providing a comparative analysis of $MgSO_4$ and aminophylline for acute asthma, using network meta-analysis to synthesize indirect evidence and guide future research. Practically, it supports clinicians in evidence-based decision-making between these adjunctive therapies, informs clinical guidelines and institutional protocols, and identifies research priorities for future head-to-head trials, ultimately aiming to improve the quality of patient care.

METHOD

Article Review Process

The review process has been systematically carried out based on Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocol. The process consists of several steps, namely 1) determining the inclusion and exclusion criteria, 2) the literature search

process, 3) screening and selection of literature results, 4) assessment of literature quality, 5) data extraction, 6) qualitative and quantitative analysis.

Search Strategy

Articles were identified from databases including PubMed, Springerlink, and Taylor & Francis. Researchers used a combination of keywords from Boolean operators, namely ("Magnesium sulfate") OR (MgSO4) AND ("Asthma exacerbation") OR ("Acute Asthma") AND (Adults). For Aminophylline, we used (Aminophylline) AND ("Asthma exacerbation") OR ("Acute Asthma") AND (Adults).

Inclusion and Exclusion Criteria

The inclusion criteria for articles reviewed by researchers include: (1) English journals; (2) Open-access. The exclusion criteria used by researchers include: (1) the topic of the article is not relevant to the study objectives; (2) The article is not a full text; (3) The article is the result of proceedings or conferences. Article eligibility checks were carried out based on the established PICO criteria (Table 1).

Table 1. PICO Criteria

Population	Adult acute asthma patient
Intervention	MgSO4 (nebulized or intravenous)
Comparison	Aminophylline
Outcome	Primary: improvement of FEV1 Secondary: improvement of PEFR, Hospital Admission Rate

Source: Developed by Researchers for Study Eligibility Criteria, 2025

Risk of Bias Assessment

To ensure the quality of selected article, we conducted risk of bias assessment with Cochrane Risk of Bias 2 for randomized trials (RoB 2). RoB 2 focussing on different aspects of trial design, conduct, and reporting.

Publication Bias

Funnel plot asymmetry testing and Egger's regression test were performed to assess the presence of publication bias. A p-value of <0.05 for Egger's test was considered as statistical evidence of significant small-study effects. Funnel plot asymmetry testing was performed if the amounts of eligible studies are adequate. Funnel plot and Egger's regression test was performed using R. Studio.

Data Collection

Data collection included the author's name and year of publication, the number and characteristics of participants, the type of intervention and its comparator, and the measurement of outcomes in both groups. Data were collected manually from selected articles, arranged in tables, then qualitative synthesis was carried out. After data extraction, we evaluated studies against the similarity assumptions required for network meta-analysis, such as patient characteristics, that would act as modifiers of relative treatment effect were similar across studies.

Statistical Analysis

All qualified article will undergo statistical analysis performed using RStudio 4.5.0. Pooled analysis was reported using forest plot. Random-effects model was used to generate standardized mean differences (SMD) and the corresponding 95% confidence interval (95%

CI). League rank table also generated to estimate the most effective agent in treating acute asthma. Test for heterogeneity among included studies was done by I-Square test, whereby I2 estimate ≥50% was indicative of substantial heterogeneity.

RESULTS AND DISCUSSION

Article Review Process

In total, 753 records were identified in the initial database search (PubMed, Springerlink, and Taylor & Francis). After primary screening, 94 articles were assessed, and 17 studies were ultimately included in this review (**Figure 1**). After data extraction, only 10 studies that eligible for quantitative analysis.

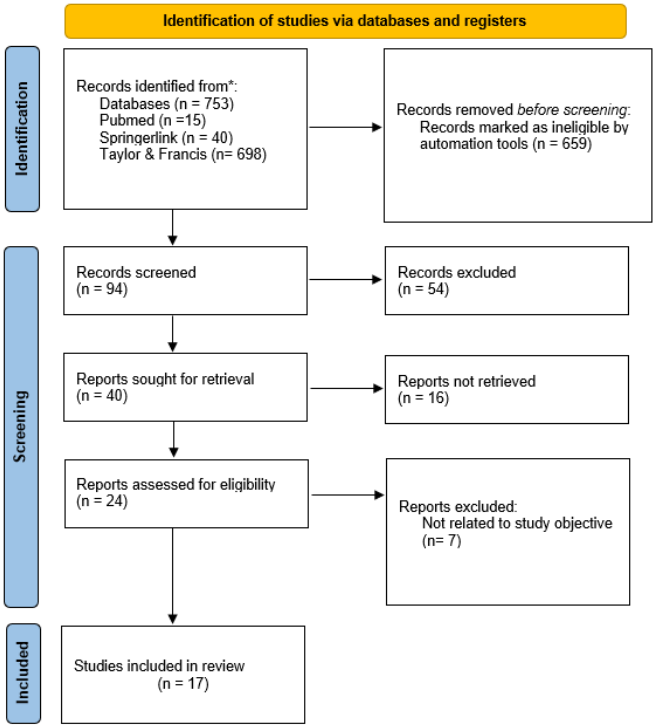

Figure 1. PRISMA flowchart of study selection

Source: Primary Data Analysis, 2025

Risk of Bias Studies

The risk of bias for every study was assessed using Cochrane Risk of Bias 2 (RoB 2) for randomized studies. Most of studies generally showed low-moderate risk of bias (**Supplementary material, Figure 1**).

Publication Bias

Egger's regression test results p=0.035, indicated some publication bias. Funnel plot was not generated due to limited study included for quantitative analysis.

Study Characteristic

A total of 957 adult patients with acute asthma were involved in this review. Five studies evaluating efficacy of aminophylline in acute asthma, while the rest focused on the role of MgSO4, either nebulized or intravenous, in acute asthma. Sample size between studies were vary. Twelve of seventeen studies used placebo as comparison. Characteristic of included studies were summarized in **Table 2**, while summary of studies was showed at **Supplementary Material, Table 1**.

Table 2. Study Characteristics

Author	Study design	Country	Sample size	Intervention	Comparison
Huang et.al, 1993 (11)	Randomized controlled trial	United Stated of America	32 patients (aminophylline = 22; Control = 11)	Intravenous aminophylline	Placebo
Montserrat et.al, 1995 (12)	Randomized controlled trial	Spain	12 patients (aminophylline = 6; Control = 6)	Intravenous aminophylline	Placebo
Ohta et.al, 1996 (13)	Randomized controlled trial	Japan	53 patients (Aminophylline = 34, Salbutamol = 19)	Intravenous aminophylline	Nebulized Salbutamol
Wrenn et.al, 1991 (14)	Randomized controlled trial	Georgia	133 patients (aminophylline = 65; Control = 68)	Intravenous aminophylline	Placebo
Self et.al, 1990 (15)	Randomized controlled trial	United Stated of America	39 patients (aminophylline = 21; Control = 18)	Intravenous aminophylline	Placebo
Bessmertny et.al, 2000 (16)	Randomized controlled trial	United Stated of America	74 patients (MgSO4 = 37; Control = 37)	Nebulized MgSO4 (384 mg in 6 mL of sterile water)	Placebo
Bloch et.al, 1995 (17)	Randomized controlled trial	United Stated of America	135 patients (MgSO4 = 67; Control = 68)	Intravenous MgSO4	Placebo
Gandia et.al, 2012 (18)	Randomized controlled trial	Tunisia	76 patients (MgSO4 only = 24; MgSO4 + Salbutamol = 12; Salbutamol = 22; Placebo = 18)	Nebulized MgSO4	Placebo, salbutamol
Hossein et.al, 2015 (19)	Randomized controlled trial	Iran	50 patients (MgSO4 = 25; Placebo = 25)	Nebulized MgSO4	Placebo
Hughes et.al, 2003 (20)	Randomized controlled trial	New Zealand	52 patients (MgSO4 = 28; Placebo = 24)	Nebulized MgSO4	Placebo
Mangat et.al, 1998 (21)	Randomized controlled trial	India	33 patients (MgSO4 = 16; Salbutamol = 17)	Nebulized MgSO4	Nebulized Salbutamol
Mohamed et.al, 2018 (22)	Randomized controlled trial	Egypt	82 patients (MgSO4 = 141; Salbutamol = 41)	Nebulized MgSO4	Nebulized Salbutamol + ipratropium bromide
Sarhan et.al, 2016 (23)	Randomized controlled trial	Egypt	30 patients (MgSO4 = 10; Salbutamol =	Nebulized MgSO4	Nebulized Salbutamol

			10; combination =10)		
Schenk et.al, 2001 (24)	Randomized controlled trial	Austria	30 patients (MgSO4 = 20; Placebo = 10)	Nebulized MgSO4	Placebo
Sharma et.al, 1994 (25)	Non-randomized controlled trial	India	18 patients	Intravenous MgSO4	Pre-treatment condition
Singh et.al, 2008 (26)	Randomized controlled trial	India	60 patients (MgSO4 = 30; Placebo = 30)	Nebulized MgSO4	Placebo
Tiffany et.al, 1993 (27)	Randomized controlled trial	United States of America	48 patients (MgSO4 bolus = 15; MgSO4 infusion = 12; Placebo = 21)	Intravenous MgSO4	Placebo

Source: Data Extraction from Included Studies, 2025

Network Analysis for Primary outcome: improvement of FEV1

We conducted a network analysis to compare the effectiveness of MgSO4 and Aminophylline in terms of FEV1 improvement. A total of 10 studies were identified, which three agents were analyzed: Aminophylline, salbutamol, and MgSO4. Due to its different administration that may influence the results, we decided to separate intravenous and nebulized MgSO4.

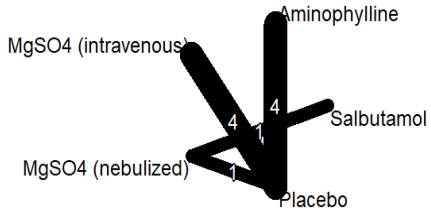

Figure 2. Network plot

Source: Primary Data Analysis, 2025

The pooled SMD for intravenous MgSO4 compared to aminophylline as 0.68 (95% CI: -1.59 – 2.95; p = 0.5573), indicating no significant difference of FEV1 improvement between those agents. Similar results also found in comparison between nebulized MgSO4 (SMD = -1.11; 95% CI = -2.73 – 0.51; p = 0.5344). Statistical heterogeneity was considered high (I^2 = 94.8%), suggesting some variation among study results.

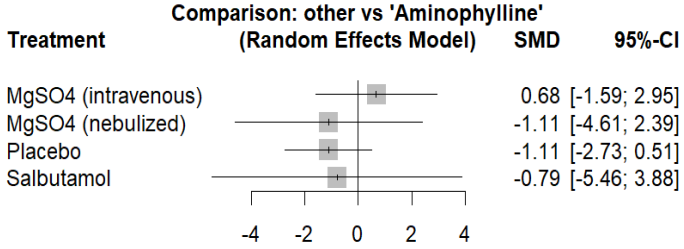

Figure 3. Pooled Analysis of FEV1 Improvement

Source: Primary Data Analysis, 2025

Figure 4 also shows the estimated ranks of effectiveness for all strategies, with associated 95% credible intervals. League rank table (**Supplementary Material, Table 2**.) show the probability of the effectiveness of each agents. In assessing its statistical significance, it can be seen from the CI if it exceeds 0, then it is not statistically significant and the magnitude of FEV1 improvement of the compared interventions can be seen from the positive or negative numbers in the league table.

The network meta-analysis demonstrated that $MgSO_4$ are not statistically significant in improvement of FEV1 compared to aminophylline. ((Nebulized MgSO4 = MD 1.11; 95% CI 0.20–3.38; p = 0.6641) (Intravenous MgSO4 = MD 1.79; 95% CI 0.20–3.38; p = 0.1797)). No significant differences were observed among active comparators, and most pairwise comparisons yielded wide confidence intervals, indicating limited precision.

Based on SUCRA ranking probabilities, placebo unexpectedly ranked highest in the treatment hierarchy, followed by nebulized MgSO4, salbutamol, aminophylline and intravenous MgSO4. This finding likely reflects imprecision, wide confidence intervals, and potential heterogeneity within the network rather than true clinical superiority. Therefore, ranking results should be interpreted cautiously.

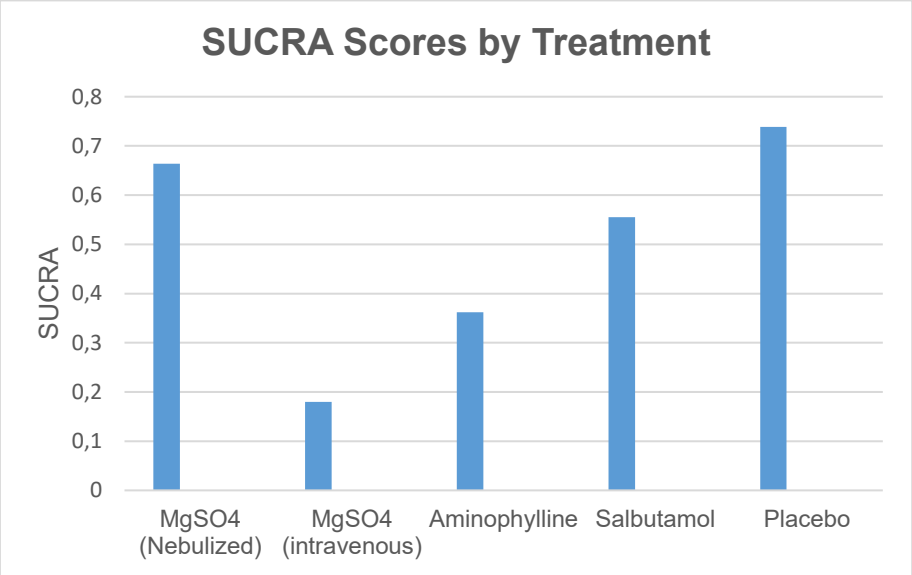

Figure 4. SUCRA Rank of Probabilities

Source: Primary Data Analysis, 2025

Secondary Outcome: Improvement of PEFR

Two studies showed no significant difference of PEFR after aminophylline administration intravenously (Huang et al., 1993; Montserrat, 1995). In contrast, some studies indicated MgSO4 nebulization efficacy in improvement of PEFR. Hossein et.al stated that compared to the control group, patients receiving nebulized MgSO4 had significantly more improvement in PEFR 20, 40 and 60 minutes after intervention (Bessmertny et al., 2002; Bloch et al., 1995). Mangat et.al and Mohamed et.al also stated similar results (Gandia et al., 2012; Hossein et al., 2016; Hughes, 2003). However, when it is compared to salbutamol, as performed in Sarhan et.al study, the difference of PEFR improvement was insignificant (Mangat et al., 1998). For intravenous MgSO4, it did not improve PEFR significantly at any

time, as stated in Tiffany et.al study. These statements implicating various results which led to uncertainty about the comparison of effectiveness between each agent.

Secondary Outcome: Hospital Admission Rate

Wrenn et.al in their study found a threefold decrease in the hospital admission rate for patients treated with aminophylline (6%) compared with placebo recipients (21%), show aminophylline may decline the needs of hospital admission (Ohta et al., 1996; Wrenn et al., 1991). However, some studies evaluating MgSO4 give various results regrarding hospital admission rate. Bloch et.al stated no significant differences in hospital admission rates between intervention and control group (Self et al., 1990). Meanwhile, Hossein et.al prove significant impact of MgSO4 administration in reducing hospital admission for acute asthma patients.

Discussion

The primary finding of our study is the absence of a statistically significant difference between MgSO4 and aminophylline regarding the improvement of FEV1. This suggest that in the acute setting, both agents provide a comparable degree of incremental bronchodilation as adjunct therapy. In these ranking analyses, nebulized MgSO4 consistently emerges with the highest probability of being the most effective therapy for improving FEV1, despite the overlapping confidence intervals observed in traditional pairwise comparisons.

The consistent finding that MgSO4 and aminophylline do not diverge significantly in their impact on FEV1 requires a careful pharmacological interpretation. Both agents are utilized as adjunct bronchodilators that work through mechanisms distinct from the primary agonist pathway (Elsakaya et al., 2018). In most clinical trials, these medications are administered to patients who have already received intensive doses of albuterol and ipratropium, alongside systemic corticosteroids (Sarhan et al., 2016). This intensive baseline therapy may induce a "ceiling effect," where the maximal achievable bronchodilation has already been largely reached, making it difficult for any additional agent to demonstrate a statistically superior spirometric improvement (Schenk et al., 2001).

Furthermore, the lack of significant difference is likely influenced by the high degree of heterogeneity among the studies. Dose variation of MgSO4 (ranging from 20 mg/kg to 75 mg/kg) and aminophylline (loading doses vs. infusions), as well as different routes (IV vs. nebulized) and evaluation time points (60 minutes to 4 hours), create a inconsistent data environment that can obscure therapeutic results differences. The average outcome reported in meta-analyses may underrepresent the true efficacy of these drugs in the most critically ill cohorts (Sharma et al., 1994).

Qualitative evaluations further distinguish these agents through secondary outcomes. Magnesium sulfate has been shown to significantly improve the peak expiratory flow rate (PEFR), a parameter often used for rapid assessment in emergency room. Conversely, aminophylline demonstrates a promising trend toward reducing hospital admission rates, a finding that stands in contrast to the inconsistent results observed with MgSO4 studies. It is imperative for clinicians to recognize that the lack of statistical significance in FEV1 differences does not imply a lack of clinical utility; rather, the ranking probabilities and distinct outcome trends provide a better insight for therapeutic selection based on specific patient needs and facility capabilities.

The ability of MgSO4 to rapidly improve PEFR suggests it is more effective than other adjuncts for the early improvement of ventilation. While FEV1 measures volume over a longer duration, PEFR captures the explosive power of the initial expiratory effort, which is more sensitive to the immediate relief of bronchospasm. This rapid physiological response can lead to an earlier reduction in the work of breathing, improvement in oxygen saturation, and a decrease in the patient's subjective sense of dyspnea (Singh et al., 2008).

This physiological improvement is crucial because PEFR reflects the caliber of the proximal airways where the most significant resistance often occurs during an acute attack. The effectiveness of magnesium in this regard is tied to its role as a natural calcium antagonist. By inhibiting the entry of calcium into the cytoplasm of bronchial smooth muscle cells, magnesium prevents the formation of the actin-myosin cross-bridges that drive contraction, leading to rapid relaxation. Furthermore, magnesium has been shown to stabilize mast cells, thereby reducing the localized release of histamine and other inflammatory mediators that trigger acute large-airway narrowing (Tiffany et al., 1993).

Some systematic reviews have found that aminophylline can reduce the risk of hospitalization (Pérez et al., 2025). This trend suggests that aminophylline may possess broader pharmacological effects that stabilize the patient’s overall clinical status beyond simple airway relaxation. One major factor is aminophylline's effect on diaphragmatic contractility and respiratory drive. In patients with severe asthma, the increased work of breathing can lead to muscular fatigue and central respiratory suppression. Aminophylline’s ability to enhance the strength of the diaphragm and stimulate the medullary respiratory centers can prevent the transition from a severe attack to respiratory failure. Additionally, its systemic hemodynamic effects, including mild pulmonary vasodilation and increased cardiac output, may improve the ventilation-perfusion matching, leading to better clinical stabilization that permits discharge rather than admission (Mohammed & Goodacre, 2007).

The use of Network Meta-Analysis is the primary strength of this study, as it allows for the integration of both direct and indirect comparisons. Since no RCTs directly compare MgSO4 and aminophylline, the NMA allows researchers to derive their relative efficacy through a common comparator, usually placebo or standard therapy. This provides a broader evidence base and more comprehensive conclusions (Healthcare Improvement Scotland, 2019).

A significant limitation in this field is the small sample size of many included trials. Many comparisons involve fewer than 100 participants, which results in wide confidence intervals and low statistical power to detect small yet clinically important differences. Furthermore, a large portion of the evidence base is derived from RCTs conducted in the 1990s. The standard of care for asthma exacerbations has transformed drastically since that time, with more emphasis on high-dose initial therapy and objective triage, which may diminish the observed efficacy of adjunctive agents in modern settings.

CONCLUSION

In summary, our study reveals no statistically significant difference exists between the MgSO4 and aminophylline for the improvement of FEV1. MgSO4 is qualitatively superior in enhancing PEFR, while aminophylline shows a promising trend toward reducing hospital

admission rates. Future high-quality head-to-head RCTs with standardized regimens are needed to clarify comparative effectiveness.

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