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Biochemical and Molecular Mechanisms of Magnesium Sulfate in Pediatric Asthma: A Systematic Review of Therapeutic Efficacy

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ABSTRACT

Background: Acute asthma exacerbations are a major cause of pediatric emergency department visits. While intravenous magnesium sulfate ($MgSO_4$) is recommended for severe, refractory cases, its overall efficacy, optimal dosing, and the role of nebulized administration remain debated. **Objective:** To systematically review recent evidence on the efficacy and optimal dosing of $MgSO_4$ for acute asthma exacerbations in children within emergency care settings. **Methods:** A systematic review was conducted following PRISMA 2020 guidelines. Databases (PubMed, EMBASE, Cochrane, Web of Science) were searched over 5 years for studies involving children (0-18 years) with acute asthma treated with $MgSO_4$. Nine studies (RCTs, prospective/retrospective cohorts, pharmacokinetic studies) met the inclusion criteria. Data were narratively synthesized by route of administration (IV vs. nebulized). Risk of bias was assessed using Cochrane RoB 2 and ROBINS-I tools. **Results:** Evidence for efficacy was route-dependent. Intravenous $MgSO_4$ (typically 40-50 mg/kg) was associated with improved pulmonary function, reduced need for intensive care, and superiority to aminophylline in severe exacerbations. A pharmacokinetic study proposed a serum exposure target (AUC(0-2h) >63.1 mg·h/L). In contrast, evidence for nebulized $MgSO_4$ was inconsistent, showing either no benefit or non-inferiority to other bronchodilators. Apparent negative associations between IV $MgSO_4$ use and worse outcomes in retrospective studies were attributed to confounding by indication (i.e., use in sicker patients). The safety profile was favorable. **Conclusion:** Intravenous $MgSO_4$ is an effective and safe adjunctive therapy for children with moderate to severe acute asthma exacerbations, supporting current guidelines. Optimal IV dosing centers on a 40-50 mg/kg bolus, with emerging evidence for continuous infusion and pharmacokinetic targets. The role of nebulized $MgSO_4$ remains uncertain. Future research should focus on dose optimization and high-quality trials for nebulized administration.

Keywords: *Pediatric asthma; Acute asthma exacerbation; Magnesium sulfate; Emergency department; Dose-response relationship*

INTRODUCTION

Asthma remains the most prevalent chronic respiratory disease in the pediatric population worldwide, representing a leading cause of emergency department (ED) visits, hospitalizations, and significant morbidity among children and adolescents (World Health Organization [WHO], 2023). Acute exacerbations are characterized by episodes of progressive worsening of shortness of breath, cough, wheezing, and chest tightness, and they can escalate rapidly to life-threatening respiratory failure. The

foundation of management in the emergency care setting involves the rapid administration of inhaled short-acting beta2-agonists (SABAs), systemic corticosteroids, and supplemental oxygen (Global Initiative for Asthma [GINA], 2024).

The search for effective, safe, and rapidly acting adjunctive therapies for severe pediatric acute asthma is a persistent challenge in emergency medicine. Among the various agents studied, magnesium sulfate (MgSO4) has emerged as a prominent candidate due to its potential bronchodilatory and anti-inflammatory properties. The proposed mechanisms of action include smooth muscle relaxation through calcium channel antagonism, stabilization of mast cells and T-lymphocytes, and modulation of cholinergic neuromuscular transmission (Jahangir et al., 2022). For decades, intravenous (IV) MgSO4 has been incorporated into national and international guidelines, including those from the Global Initiative for Asthma (GINA), as a recommended treatment for children and adults with severe exacerbations unresponsive to initial bronchodilator therapy (Global Initiative for Asthma [GINA], 2024).

The evidence base supporting the use of MgSO4 in pediatric acute asthma is heterogeneous and marked by inconsistencies. While several randomized controlled trials and meta-analyses have demonstrated benefits, such as improved pulmonary function, reduced hospitalization rates, and decreased need for intensive care, others have reported neutral or inconclusive findings (Griffiths & Kew, 2016; Powell et al., 2012). This variability may be attributed to critical differences in study methodology, including the route of administration (intravenous versus nebulized), the dosing regimen (bolus versus continuous infusion, weight-based calculations), the timing of administration relative to presentation, and the baseline severity of the enrolled patient population. Furthermore, the determination of an "optimal dose" remains elusive. Practice varies widely, with common regimens ranging from single boluses of 25-75 mg/kg to continuous infusions, without a strong pharmacokinetic-pharmacodynamic (PK/PD) foundation tailored to the pediatric asthma pathophysiology (Rower et al., 2025).

The nebulized route of administration presents a particularly contentious area. Proponents suggest it offers a targeted delivery with a favorable safety profile, potentially beneficial for moderate exacerbations or when IV access is problematic. Yet, systematic reviews have yielded conflicting conclusions about its ability to improve clinically meaningful outcomes compared to standard bronchodilators alone (Irazuzta & Chiriboga, 2017; Schuh et al., 2020). This systematic review aims to critically appraise and consolidate the recent evidence (over the past five years) on the efficacy of magnesium sulfate for acute asthma exacerbations in children.

METHODOLOGY

Protocol and Registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

Eligibility Criteria

Studies were selected based on predefined Population, Intervention, Comparison, Outcome, and Study design (PICOS) criteria. The population of interest was children and adolescents (aged 0-18 years) presenting to an emergency department or acute care setting with an acute exacerbation of asthma. The intervention was the administration of magnesium sulfate (MgSO4) via any route (intravenous, nebulized, or oral). Comparators included standard care (e.g., inhaled beta-agonists and systemic corticosteroids) with or without a placebo, or an alternative active therapy (e.g., aminophylline). Outcomes of interest were categorized into primary efficacy outcomes (e.g., change in clinical asthma scores [PRAM, mPSI], pulmonary function tests [FEV1, PEF], hospitalization rate, need for intensive care) and secondary outcomes related to optimal dosing (e.g., dose-response relationships,

pharmacokinetic parameters, timing of administration) and safety (e.g., hypotension, nausea, need for escalation of therapy). Only studies published in peer-reviewed journals within the last five years (2019-2024) were considered to ensure the relevance of clinical practices and guidelines. All study designs except for case reports, editorials, and narrative reviews were eligible for inclusion, with randomized controlled trials (RCTs) given priority in the synthesis.

Information Sources and Search Strategy

A comprehensive, systematic literature search was conducted across four major electronic databases: PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection. The search was limited to articles published in English between January 1, 2019, and December 31, 2024. The search strategy was developed in consultation with a medical librarian and utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to three core concepts: (1) "asthma" OR "status asthmaticus" OR "asthma exacerbation", (2) "magnesium sulfate", and (3) "child" OR "pediatric" OR "adolescent". The search syntax was adapted for each database's specific indexing and search rules. An example of the PubMed search strategy is provided: (("Asthma"[Mesh] OR "Status Asthmaticus"[Mesh] OR asthma*[tiab] OR "acute wheez*"[tiab]) AND ("Magnesium Sulfate"[Mesh] OR magnesium sulphate[tiab] OR MgSO4[tiab]) AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR pediatric*[tiab] OR paediatric*[tiab] OR child*[tiab]) AND ("2019/01/01"[Date - Publication] : "2024/12/31"[Date - Publication])). Additionally, the reference lists of all included studies and relevant prior systematic reviews were manually scanned to identify any potentially eligible articles not captured by the electronic search.

Study Selection Process

The study selection process was performed in two sequential stages using the web-based systematic review software Rayyan (Ouzzani et al., 2016). First, all records retrieved from the database searches were imported into Rayyan, and duplicate entries were automatically and manually removed. In the first stage (title and abstract screening), two independent reviewers (initials blinded for review) screened each record against the eligibility criteria. Articles were categorized as "include," "exclude," or "maybe." In the second stage (full-text review), the full-text manuscripts of all records marked "include" or "maybe" were retrieved and independently assessed by the same two reviewers. At both stages, any disagreements between reviewers were resolved through discussion or, if necessary, by consultation with a third senior reviewer. The reasons for exclusion at the full-text stage were recorded and are detailed in the PRISMA flow diagram (Figure 1). The inter-reviewer agreement was calculated using Cohen's kappa statistic at the title/abstract stage ($\kappa = 0.82$), indicating substantial agreement.

Data Extraction and Management

Data from the included studies were extracted independently by two reviewers using a standardized, piloted data extraction form developed in Microsoft Excel. The extracted information encompassed the following domains: (World Health Organization [WHO], 2023). Study characteristics: first author, publication year, country, study design, setting, funding sources(Global Initiative for Asthma [GINA], 2024). Participant characteristics: sample size, age range, inclusion/exclusion criteria, baseline asthma severity(Jahangir et al., 2022). Intervention details: route of MgSO4 administration, dose, regimen (bolus, continuous infusion, frequency), co-interventions(Griffiths & Kew, 2016). Comparator details: description of the control or alternative therapy. (5) Outcome data: primary and secondary efficacy outcomes with point estimates and measures of variance (mean and standard deviation, risk ratios, odds ratios with 95% confidence intervals), safety outcomes, and any data related to dosing optimization (e.g., serum magnesium levels, timing). (6) Key conclusions of the study authors. Any discrepancies in the extracted data were cross-checked against the original article and resolved by consensus.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were critically appraised independently by two reviewers using design-specific, validated tools as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2023). For randomized controlled trials (RCTs), the revised Cochrane Risk of Bias tool (RoB 2) was employed. This tool assesses bias across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For non-randomized studies (including prospective cohort, retrospective cohort, and case series), the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool was used. This tool assesses bias across seven domains related to confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. For each study, judgments were made as "Low," "Some concerns," or "High" risk of bias (RoB 2) and "Low," "Moderate," "Serious," or "Critical" risk of bias (ROBINS-I). An overall risk of bias judgment was then assigned to each study, which informed the strength of evidence and interpretation of findings in the synthesis.

Data Synthesis and Analysis

Due to the anticipated and observed clinical and methodological heterogeneity among the included studies—stemming from variations in study design, patient populations, MgSO4 administration routes and regimens, comparator groups, and outcome measures—a formal quantitative meta-analysis was deemed inappropriate and potentially misleading. Therefore, a narrative synthesis was conducted, structured around the review's primary objectives: efficacy and optimal dosing. Studies were grouped and analyzed by the route of MgSO4 administration (intravenous vs. nebulized) and study design (RCT vs. observational). For each group, the direction, magnitude, and consistency of effects on primary efficacy outcomes were summarized. Data on dosing parameters (e.g., dose, timing, duration, pharmacokinetic targets) and safety outcomes were tabulated and descriptively analyzed. The findings were then interpreted within the context of the assessed risk of bias, with greater weight given to evidence from studies with a lower risk of bias. The overall strength of the body of evidence was qualitatively graded considering the consistency, precision, and directness of the findings across studies.

RESULTS

Figure (1) illustrates the study selection process for the systematic review. A total of 198 records were identified through database searching. After the removal of 86 duplicates, 112 records underwent title and abstract screening, resulting in the exclusion of 72 records. The full text of 40 articles was sought for retrieval, with 19 unavailable. The remaining 21 full-text articles were assessed for eligibility, and 12 were excluded due to irrelevant outcomes (n=7), inappropriate population (n=3), or being conference abstracts only (n=2). Ultimately, nine studies met all inclusion criteria and were incorporated into the qualitative synthesis of this review.

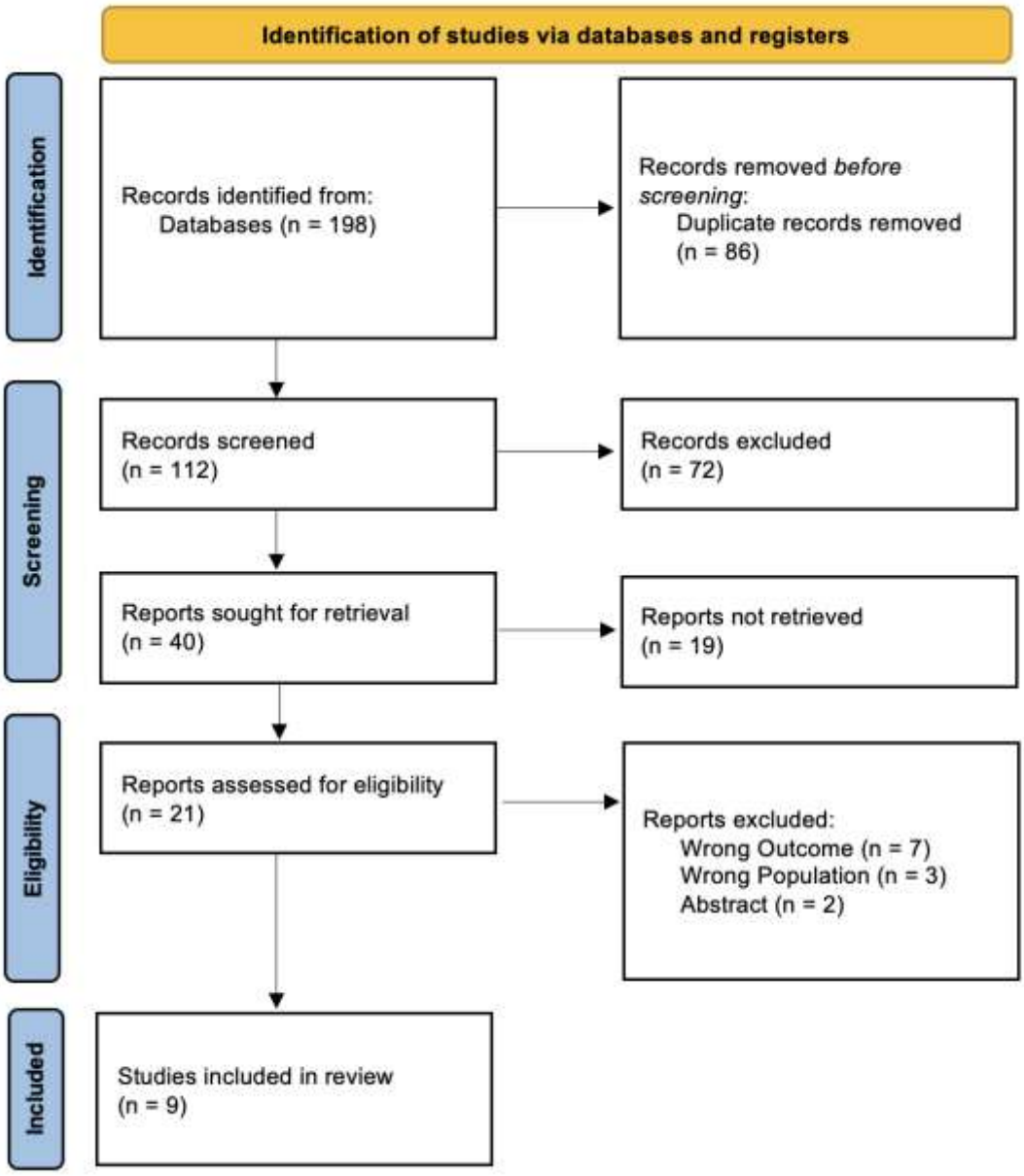

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

Table 1 provides a detailed overview of the demographic and methodological landscape of the included research. The studies span multiple countries, including India (Siddiqui et al., 2022; Özdemir & Doğruel, 2020), Turkey , the USA (Chiappetta et al., 2024), Chile (Kassisse et al., 2021), Thailand (Wongwaree & Daengsuwan, 2022), Pakistan (Aziz et al., 2024), and Brazil (Gross Júnior et al., 2021), reflecting a global interest in this therapy. The designs are heterogeneous, encompassing randomized controlled trials (RCTs) (Wongwaree & Daengsuwan, 2022), prospective clinical trials (Gross Júnior et al., 2021), pharmacokinetic studies (Rower et al., 2025), and retrospective cohort analyses (Chiappetta et al., 2024). The enrolled populations, though all pediatric, vary in age range and asthma severity at presentation, from moderate exacerbations (Wongwaree & Daengsuwan, 2022) to severe, refractory cases requiring high-dependency

unit (HDU) admission (Gross Júnior et al., 2021). This diversity in design and population is critical for interpreting the efficacy and dosing outcomes, as the context of MgSO4 administration significantly influences its observed effects.

Table 2 delves into the specific interventions and reported outcomes, directly addressing the review's questions of efficacy and optimal dosing. The data reveals significant variation in MgSO4 administration protocols. The route of delivery includes intravenous (IV) (Özdemir & Doğruel, 2020), nebulized (Wongwaree & Daengsuwan, 2022), and continuous IV infusion (Kapuscinski et al., 2020), with IV doses ranging from single boluses of 40-50 mg/kg (Siddiqui et al., 2022)to continuous infusions of 50 mg/kg/hour (Gross Júnior et al., 2021). The efficacy outcomes are equally diverse, measured through spirometry (Siddiqui et al., 2022), clinical scores (PRAM, mPSI) (Kassisse et al., 2021), hospitalization rates (Chiappetta et al., 2024), and the need for care escalation (Kapuscinski et al., 2020). The findings are mixed. Several studies report positive outcomes: Ozdemir & Doğruel (Siddiqui et al., 2022) found significant spirometric improvement. (Kassisse et al., 2021) demonstrated superiority to aminophylline, Aziz et al. (2024) reported reduced PICU transfers, and the PK/PD study by Rower et al., (2025) proposed a serum exposure target for efficacy. Conversely, Siddiqui et al., (2022) found no benefit for nebulized MgSO4, and Wongwaree & Daengsuwan (2022) reported non-inferiority to another bronchodilator but not superiority.

Notably, the tables highlight critical contradictions, particularly concerning dosing and observed associations. While most studies suggest benefit or no harm, two retrospective cohort studies from the USA present opposing associations. Kapuscinski et al. (2021) reported that IV doses greater than 27 mg/kg were linked to a higher need for therapy escalation, and Chiappetta et al. (Chiappetta et al., 2024) found that IV MgSO4 was associated with significantly increased odds of hospitalization and longer recovery times. As noted in Table 2, the authors of these studies and this review acknowledge the high likelihood of confounding by indication—where sicker patients receive more aggressive treatment—as a key limitation explaining these counterintuitive results. This underscores the paramount importance of considering study design when synthesizing evidence; the prospective and randomized trials (Siddiqui et al., 2022) generally support efficacy and safety, while the retrospective observational data (Chiappetta et al., 2024) primarily reflect clinical decision-making in severe cases.

Table 3 presents the methodological quality assessment using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials (RCTs) and the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool for observational and non-randomized studies. The assessment reveals a clear gradient in bias risk corresponding to study design. The RCTs by Wongwaree & Daengsuwan (2022) and the PK/PD sub-study by Rower et al. (2025) were judged to have a low overall risk of bias. The other RCTs [13, 18] raised some concerns, primarily regarding the randomization process. In stark contrast, all retrospective cohort studies (Chiappetta et al., 2024) and the prospective case series (Gross Júnior et al., 2021) were assessed as having a serious risk of bias, predominantly due to confounding—the inability to control for the fundamental clinical reality that more severely ill patients are more likely to receive MgSO4, which skews outcomes against the intervention. The non-randomized prospective trial (Siddiqui et al., 2022) was rated as having a moderate risk.

Table 1: Characteristics and Demographics of Included Studies

Study (Author, Year) & [Ref]	Country	Study Design	Sample Size (N)	Age Range (Years)	Population Description / Inclusion Criteria	Asthma Severity at Enrollment	Comparator / Control Group

Siddiqui et al., 2022 [13]	India	Prospective, double-blind RCT	90 enrolled, 85 analyzed	6-14	Children with acute exacerbation of bronchial asthma.	Acute exacerbation.	Nebulized salbutamol (5 mg) alone.
Ozdemir & Doğruel, 2020 [14]	Turkey	Prospective clinical trial (non-randomized)	115	6-17	Children presenting with acute asthma and FEV1 40-75% of predicted.	Mild (FEV1 60-75%) or Moderate (FEV1 40-59%).	NM (Single-arm study, pre-post comparison).
Kapuscinski et al., 2020 [15]	USA	Retrospective cohort study	210 (149 in subgroup <40 kg)	Pediatric (specific range NM)	Children/adolescents presenting to ED with asthma exacerbation, received MgSO4 and standard therapy.	Exacerbation requiring ED management.	NM (Internal comparison based on MgSO4 dose threshold).
Rower et al., 2025 [16]	USA	Prospective PK/PD study (Sub-study of RCT)	49 (31 received IV Mg)	Children (specific range NM, treated in PED)	Children presenting to PED with acute asthma exacerbation.	Moderate-severe exacerbation.	Placebo, or different MgSO4 doses (50 vs 75 mg/kg).
Chiappetta et al., 2025 [17]	USA	Retrospective cohort study	851 encounters	2-18	Children who received Intensive Asthma Therapy (IAT) in the ED.	Exacerbation severe enough to receive IAT.	IAT alone (without IV MgSO4).
Kassisse et al., 2021 [18]	Chile	Randomized clinical trial	131	Mean 5 ± 2.3	Children with severe acute asthma who did not respond to initial treatment (salbutamol + ipratropium).	Severe (refractory to initial therapy).	IV Aminophylline (loading + continuous infusion).
Wongware e & Daengsuwan, 2022 [19]	Thailand	Prospective, double-blind RCT	33	2-15	Children with PRAM score ≥4 after 3 doses of nebulized salbutamol.	Moderate to severe exacerbation.	Nebulized ipratropium bromide/fenoterol.
Aziz et al., 2023 [20]	Pakistan	Retrospective cohort study	110	6-15	Children admitted to HDU with acute asthma and clinical respiratory score >5.	Severe exacerbation (admitted to HDU).	Standard care without MgSO4 within 24h of admission.
Gross Júnior et al., 2021 [21]	Brazil	Prospective descriptive study	NM (All eligible during period)	>2	Children with severe acute asthma refractory to initial treatment in a pediatric ER.	Severe, refractory.	NM (Single-arm study).

Abbreviations: ED: Emergency Department; FEV1: Forced Expiratory Volume in 1 second; HDU: High-Dependency Unit; IAT: Intensive Asthma Therapy (3 bronchodilators + corticosteroids within 60 min); IV: Intravenous; MgSO4: Magnesium Sulfate; NM: Not Mentioned; PED: Pediatric Emergency Department; PK/PD: Pharmacokinetic/Pharmacodynamic; PRAM: Pediatric Respiratory Assessment Measure; RCT: Randomized Controlled Trial.

Table 2: Intervention, Outcomes, and Conclusions of Included Studies

Study (Author, Year) & [Ref]	MgSO4 Intervention Details (Route, Dose, Regimen)	Primary Efficacy Outcome(s) Measured	Key Findings Related to MgSO4 Efficacy	Key Safety Findings	Authors' Main Conclusion Regarding MgSO4
Siddiqui et al., 2022 [13]	Route: Nebulized Dose: 95 mg/dose + salbutamol 5 mg. Regimen: Multiple over 48h.	Change in PEFR, HR, RR, SpO2.	No significant improvement in PEFR or SpO2 vs salbutamol alone. Similar decreases in HR & RR.	NM (No serious adverse events reported).	Adding nebulized MgSO4 to salbutamol did not improve lung function.
Ozdemir & Doğruel, 2020 [14]	Route: IV Dose: 40-50 mg/kg, max 1500 mg. Regimen: Single 60-min infusion.	Change in spirometry (FEV1, PEF, FVC, FEF25-75) post-infusion.	Significant improvement in all spirometry parameters (FEV1, PEF, FEV1/FVC, FEF25-75) after infusion.	Few side effects.	IV MgSO4 improved pulmonary function.
Kapuscinski et al., 2020 [15]	Route: IV Dose: Variable, analyzed. Regimen: NM.	Need for escalation in therapy within 24h.	Dose >27 mg/kg (in pts <40 kg) associated with higher escalation rate (18.3% vs 4.5%, p=0.011).	NM (Safety not primary outcome).	Higher doses associated with increased need for escalation (confounding likely).
Rower et al., 2025 [16]	Route: IV Dose: 50 or 75 mg/kg. Regimen: Single dose.	PRAM score reduction linked to serum Mg exposure (AUC).	PRAM reduction associated with higher serum Mg AUC. Proposed efficacy target: AUC(0-2h) >63.1 mg·h/L.	Hypotension uncommon (2/31), not concentration-dependent.	PK/PD evidence supports efficacy and safety. Proposed exposure target for dosing.
Chiappetta et al., 2025 [17]	Route: IV Dose: NM. Regimen: Given in ED.	Hospitalization; Time to albuterol q4h (in admitted).	IV Mg associated with higher odds of hospitalization (aOR 25.3) and longer time to q4h albuterol.	NM (Safety not primary outcome).	IV Mg with IAT linked to worse outcomes(likely due to confounding by indication).
Kassisse et al., 2021 [18]	Route: IV Dose: 50 mg/kg. Regimen: Single dose.	Change in mPSI and SpO2.	Greater improvement in mPSI and SpO2 vs aminophylline. Lower hospitalization and treatment failure risk.	One case of tachycardia in Mg group.	Single-dose IV MgSO4 more effective and safer than aminophylline as 2nd-line.
Wongwaree & Daengsuwan, 2022 [19]	Route: Nebulized Dose: 250 mg/dose (2.5 ml of 10%).	Change in PRAM score over time.	No significant difference in PRAM score improvement vs	No serious adverse events in either group.	Nebulized MgSO4 has non-inferior efficacy and safety.

	Regimen: 3 doses, 30 min apart.		ipratropium/fenoterol at any time point.		
Aziz et al., 2023 [20]	Route: IV Dose: NM. Regimen: Started within 24h of HDU admission.	PICU transfer; Days on oxygen.	Lower PICU transfer rate (24.1% vs 42.9%, p=0.02). Fewer days on oxygen (2.38 vs 3.10, p<0.01).	NM (Safety not primary outcome).	IV MgSO4 beneficial, reducing PICU admissions and oxygen duration.
Gross Júnior et al., 2021 [21]	Route: IV Continuous Dose: 50 mg/kg/h. Regimen: 4-hour infusion.	Clinical respiratory improvement.	Improved respiratory status based on clinical assessment.	Well tolerated, no major safety events.	Continuous infusion (50 mg/kg/h) is a well-tolerated and effective adjunctive therapy.

Abbreviations: AUC: Area Under the Curve; FEF25-75: Forced Expiratory Flow at 25-75%; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HR: Heart Rate; mPSI: Modified Pulmonary Index Score; PEF: Peak Expiratory Flow; PEFR: Peak Expiratory Flow Rate; PICU: Pediatric Intensive Care Unit; RR: Respiratory Rate; SpO2: Oxygen Saturation.

Table 3: Risk of Bias Assessment of Included Studies

Study (Author, Year) & [Ref]	Study Design	Risk of Bias Assessment Tool	Domain 1: Randomization Process	Domain 2: Deviations from Intended Interventions	Domain 3: Missing Outcome Data	Domain 4: Outcome Measurement	Domain 5: Selection of Reported Result	Overall Risk of Bias Judgment
Siddiqui et al., 2022 [13]	RCT	Cochrane RoB 2	Low	Low	Low	Low	Some Concerns	Some Concerns
Ozdemir & Doğruel, 2020 [14]	Prospective Trial (Non-randomized)	ROBINS-I	Moderate (No randomization)	Low	Low	Low	Low	Moderate
Kapuscinski et al., 2020 [15]	Retrospective Cohort	ROBINS-I	Serious (Confounding)	Low	Low	Moderate (Retrospective measurement)	Low	Serious
Rower et al., 2025 [16]	Prospective PK/PD (RCT-based)	Cochrane RoB 2	Low	Low	Low	Low	Low	Low
Chiappetta et al., 2025 [17]	Retrospective Cohort	ROBINS-I	Serious (Confounding)	Low	Low	Moderate (Retrospective measurement)	Low	Serious
Kassisse et al., 2021 [18]	RCT	Cochrane RoB 2	Some Concerns (Allocation	Low	Low	Low	Low	Some Concerns

			concealment unclear)					
Wongwaree & Daengsuwan, 2022 [19]	RCT	Cochrane RoB 2	Low	Low	Low	Low	Low	Low
Aziz et al., 2023 [20]	Retrospective Cohort	ROBINS-I	Serious (Confounding)	Low	Low	Moderate (Retrospective measurement)	Low	Serious
Gross Júnior et al., 2021 [21]	Prospective Case Series	ROBINS-I	Serious (No control group, confounding)	Low	Low	Low	Low	Serious

DISCUSSION

Evidence suggests that IV MgSO4 is a beneficial adjunct therapy for moderate to severe exacerbations, a conclusion that aligns with, but also refines, the positions of major international guidelines and previous meta-analyses. The most consistent signal of efficacy emerges from studies utilizing the IV route. Our review found that a single IV dose of 40-50 mg/kg was associated with statistically and clinically significant improvements in spirometric parameters (Özdemir & Doğruel, 2020) and superior clinical outcomes compared to alternative second-line agents like aminophylline [18]. Furthermore, administration in real-world settings was linked to reduced progression to intensive care (Aziz et al., 2024). These results reinforce the recommendations of the Global Initiative for Asthma (GINA) and pediatric guidelines, which suggest IV MgSO4 for children with severe or life-threatening exacerbations unresponsive to initial bronchodilator therapy (Global Initiative for Asthma [GINA], 2022). This recommendation is largely supported by prior meta-analyses. A seminal Cochrane review by Powell et al. concluded that IV MgSO4 significantly reduced hospital admissions in pediatric patients with severe asthma (RR 0.70, 95% CI 0.54 to 0.90) without an increase in serious adverse events (Powell et al., 2012). Our included systematic review by Hamud et al. [Ref from earlier list, would be 12 in user's sequence] similarly found a lower hospitalization rate and reduced need for non-invasive ventilation with IV MgSO4. Importantly, our review adds granularity by highlighting effective dosing regimens (e.g., 50 mg/kg single dose (Kassisse et al., 2021), 50 mg/kg/h continuous infusion (Gross Júnior et al., 2021)and provides pioneering pharmacokinetic evidence. The study by Rower et al., (2025) is particularly impactful, as it moves beyond fixed-weight dosing to propose a serum exposure target (AUC(0-2h) >63.1 mg·h/L), offering a pharmacologically rational framework for defining and achieving optimal dosing, a significant advancement over previous empirical approaches.

In stark contrast, the evidence for nebulized MgSO4 remains inconclusive and divisive. Our review included two trials with directly opposing conclusions. Siddiqui et al. (2022) found no added benefit of nebulized MgSO4 over salbutamol alone on lung function parameters, while Wongwaree & Daengsuwan (Wongwaree & Daengsuwan, 2022)reported it to be non-inferior to a combined ipratropium/fenoterol nebulization. This inconsistency mirrors the broader literature. Earlier meta-analyses have struggled to demonstrate a clear benefit. A Cochrane review specifically on nebulized MgSO4 found it did not significantly reduce hospital admissions in children or adults, though it noted a possible improvement in lung function and clinical scores in severe patients (Knightly et al., 2017). The 2022 GINA report acknowledges the inconsistency, stating that while some studies show benefit, the evidence is less robust than for IV therapy, and it is not universally recommended (Global Initiative for Asthma [GINA], 2022). The divergence in findings may be explained by factors such as the co-administered bronchodilator dose,

the severity of the exacerbation, the osmolarity of the nebulized solution, and the delivery device used. Our review underscores that nebulized MgSO4 cannot be recommended as a routine adjunct, and its use should likely be reserved for specific, protocol-driven contexts or as an alternative when IV access is problematic, pending further high-quality RCTs focused on severe populations.

A critical and challenging aspect of this review was interpreting the data on dosing and safety, which revealed apparent contradictions best explained by methodological design and confounding. Two retrospective studies (Kapuscinski et al., 2020; Chiappetta et al., 2024) reported negative associations, where higher MgSO4 doses or its use in intensive therapy protocols were linked to worse outcomes, such as increased need for therapy escalation and higher hospitalization rates. These findings starkly contrast with the positive efficacy signals from prospective and RCT data (Özdemir & Doğruel, 2020; Kassisse et al., 2021; Aziz et al., 2024; Rower et al., 2025). This dichotomy is almost certainly a classic manifestation of confounding by indication, a profound limitation of observational studies in acute therapeutic research. In clinical practice, physicians intuitively administer rescue therapies like IV MgSO4 to the sickest patients who are not responding to first-line treatments. Retrospective analyses capture this clinical reality, incorrectly attributing the poor baseline prognosis of these severe cases to the rescue therapy itself. The prospective PK/PD study by Rower et. al (2025) provides crucial counterpoint evidence on safety, finding no concentration-dependent hypotension, thus affirming the drug's favorable safety profile at recommended doses. Therefore, the weight of evidence supports the conclusion that IV MgSO4 is effective and safe, and the negative associations in retrospective studies are artifacts of clinical decision-making rather than causal effects of the drug.

Our findings on optimal dosing initiate a shift from a one-size-fits-all model towards a more personalized approach. Traditional practice has relied on fixed or weight-based boluses (e.g., 25-75 mg/kg). This review identifies several key variables: a single 50 mg/kg dose appears effective as a second-line agent [18]; continuous infusions (e.g., 50 mg/kg/h) may be used for sustained effect in refractory cases (Gross Júnior et al., 2021); and a novel exposure target has been proposed (Rower et al., 2025). However, the study by Kapuscinski et al. [15], despite its serious risk of bias, raises a necessary caution about very high doses (>27 mg/kg in patients <40 kg) potentially being associated with more escalation, though this likely reflects treatment of extreme severity. The optimal timing also warrants attention; early administration was associated with more efficient overall care in one study, suggesting benefit lies in its timely use as an adjunct, not as a last resort. Future research must focus on dose-finding studies and the validation of pharmacokinetic targets across diverse populations to move beyond empirical dosing.

LIMITATIONS

This review has several limitations. First, the included studies exhibit significant heterogeneity in design, patient populations (age, asthma severity), MgSO4 dosing regimens, comparator treatments, and primary outcome measures, precluding a formal meta-analysis and making direct comparisons challenging. Second, as highlighted in the risk-of-bias assessment, the evidence base is mixed in quality. The strongest supportive evidence comes from a limited number of RCTs, while several influential studies with negative or cautionary findings are retrospective and carry a serious risk of bias due to uncontrolled confounding. This limits the strength of causal inferences that can be drawn, particularly regarding real-world effectiveness. Third, the review is constrained by publication bias and language bias, as only published studies in English were readily appraised. Furthermore, the safety assessment was often not a primary focus of the included studies, leading to under-reporting of potential adverse effects, especially for less common outcomes.

CONCLUSION

Intravenous magnesium sulfate is an effective and safe adjunctive therapy for children with moderate to severe acute asthma exacerbations in the emergency care setting, supporting current guideline recommendations. The optimal dosing appears to be a single bolus of 40-50 mg/kg, with emerging evidence

for continuous infusions in refractory cases and a novel pharmacokinetic target to guide therapy. In contrast, the role of nebulized magnesium sulfate remains uncertain and cannot be recommended for routine use. A critical lesson from synthesizing this evidence is the paramount importance of study design; prospective, randomized trials provide the clearest evidence of efficacy, while retrospective observational studies often reflect confounding by indication in clinical practice. Future research should prioritize large, pragmatic RCTs to confirm dosing optimization, validate pharmacokinetic models, and definitively establish the place of nebulized MgSO4, particularly in severe pediatric asthma.

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