

Intravenous Magnesium Sulfate Treatment for Acute Asthma in the Emergency Department: A Systematic Review of the Literature

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Study objectives: There is some evidence that magnesium, when infused into asthmatic patients, can produce bronchodilation in addition to that obtained from standard treatments. This systematic review examined the effect of intravenous magnesium sulfate used for patients with acute asthma managed in the emergency department.

Methods: Only randomized controlled trials were eligible for inclusion. Studies were included if patients presented with acute asthma and were treated with intravenous magnesium sulfate versus placebo. Trials were identified from the Cochrane Airways Review Group register, which consists of a combined search of EMBASE, MEDLINE, and CINAHL databases and hand-searching of 20 key respiratory journals. Bibliographies from included studies and known reviews were searched. Primary authors and content experts were contacted. Data were extracted and methodologic quality was assessed independently by 2 reviewers. Missing data were obtained from authors.

Results: Seven trials (5 adult, 2 pediatric) involving a total of 668 patients were included. Overall, admission to hospital was not statistically reduced using magnesium sulfate (odds ratio [OR] 0.31, 95% confidence interval [CI] 0.09 to 1.02). In the severe subgroup, admissions were reduced in those receiving magnesium sulfate (OR 0.10, 95% CI 0.04 to 0.27). Overall, patients receiving magnesium sulfate demonstrated nonsignificant improvements in peak expiratory flow rates (PEFR) when all studies were pooled (weighted mean difference [WMD] 29 L/min, 95% CI -3 to 62). In studies of patients with severe acute asthma, PEFR WMD improved by 52 L/min (95% CI 27 to 78) favoring magnesium sulfate treatment. The absolute FEV₁ also improved by 10% predicted (95% CI 4 to 16) in patients with severe acute asthma. No clinically important changes in vital signs or side effects were reported.

Conclusion: Current evidence does not clearly support routine use of intravenous magnesium sulfate in all patients with acute asthma presenting to the ED. However, magnesium sulfate appears to be safe and beneficial for patients who present with severe acute asthma. Practice guidelines need to be changed to reflect these results.

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INTRODUCTION

Asthma affects approximately 7% of adults in North America,¹⁻⁴ and patients frequently present to the emergency department with acute asthma. Acute presentations to EDs in North America are common and potentially serious complications of asthma. Approximately 10% to 20% of patients who present to the ED will require admission to the hospital, and this rate varies depending on factors such as disease severity,⁵ the treatments received,⁶ and the setting.⁷ The annual costs for asthma in the United States approximate \$6 billion³; in Canada, annual costs approximate \$600 million.⁸ Moreover, in Canada, acute care costs account for approximately 20% of these costs.⁸

Our understanding of asthma has improved over the past decade,⁹⁻¹¹ and there is now general agreement on the primary role of inflammation in the pathophysiology of asthma. Control of inflammation has become the cornerstone of treatment during acute asthma.^{12,13} Despite this, practice variation exists with respect to treatment approaches¹⁴; this may be due in part to a lack of primary research and evidence-based reviews relevant both to the ED setting and the field at large.¹⁵

Generally, the initial treatment agents include β -agonists that specifically target adrenergic receptors.^{12,13} Among children¹⁶⁻¹⁸ and adults,¹⁹ anticholinergic agents (eg, ipratropium bromide) administered in conjunction with β -agonists have been shown to potentially increase the magnitude and duration of bronchodilation over that achieved with β -agonists alone. Additional treatment of airway edema is usually initiated with systemic corticosteroids.⁶

Given the need for rapid bronchodilation, there has been a focus on the use of β -agonists in the initial management of acute asthma.²⁰ However, the potential role of other agents in the initial management of acute asthma is

still unclear. Meta-analyses have failed to demonstrate a benefit to aminophylline in acute asthma for adults²¹ and children.²² On the other hand, steroids appear to reduce hospital admissions.⁶ Significant debate exists with respect to the benefit of other agents such as magnesium sulfate in the treatment of acute asthma.

Magnesium, a predominantly intracellular cation, is an important cofactor in many enzymatic reactions and is linked to cellular homeostasis.²³ In addition, magnesium has an effect on smooth muscle cells, with hypomagnesemia causing contraction and hypermagnesemia causing relaxation. There is some evidence that when magnesium is infused into asthmatic patients, it produces additional bronchodilation.^{24,25} Because magnesium levels in asthmatics appear to be similar to those in control subjects,²⁶ the effect may relate to magnesium's competitive antagonism with calcium.²⁷ In addition, evidence suggests that magnesium may reduce the neutrophilic burst associated with the inflammatory response in asthma.²⁸ Thus, there is reason to believe that magnesium treatment, in the form of intravenous magnesium sulfate, may be beneficial in the treatment of acute asthma.

This systematic overview examines evidence for the effectiveness of intravenous magnesium sulfate treatment in acute asthma. Although descriptive reviews of magnesium do exist,²⁹ no systematic review of the magnesium sulfate literature has been published to date. The objective of this meta-analysis was to determine the effect of intravenous magnesium sulfate therapy for patients with acute asthma treated in the ED. The specific aims of the review were to quantify the effect of the combination of magnesium sulfate with other agents compared with the effect of these other agents alone.

MATERIALS AND METHODS

Before the start of the research, a protocol was developed to reduce the influence of bias in the review. In this protocol, criteria for study inclusion were clearly outlined. All of the following criteria needed to be present for the study to be included in the review:

1. Design: All reported studies had to be randomized controlled trials (RCTs).
2. Population: Studies including either children or adult patients presenting to an ED for treatment of acute asthma were considered for inclusion in the overview. Age was one of the subgroups examined in this review.
3. Intervention: Studies reporting results of patients randomly assigned to receive magnesium sulfate compared with placebo early (ie, all within 90 minutes of

arrival) in the ED treatment were included. Because patients with acute asthma require additional treatments (eg, β -agonists, corticosteroids, ipratropium bromide), data for any cointerventions were recorded or requested from the authors when not reported in the studies.

4. Outcomes: All patient outcomes were considered; however, the primary dichotomous outcome was admission to hospital.

Secondary outcomes included:

1. Pulmonary function tests including: peak expiratory flow rates (PEFRs), forced expiratory volume in 1 second (FEV_1), and % predicted PEFR or FEV_1
2. Vital signs (heart rate, respiratory rate, blood pressure)
3. Adverse outcomes and side effects

A comprehensive approach to identifying potential studies involving a number of search strategies was used. First, the Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheez* RCT" register through a comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, handsearching of 20 common respiratory care journals has been completed and relevant RCTs have been added to the register. Finally, the register is updated with searches of Cochrane Controlled Trials Register (CCTR), the Cochrane Collaboration's RCT register. The ARG register contains a variety of studies published in foreign languages, and trials were not excluded on the basis of language. The current overview includes ARG register updates to January 1999.

Search of the ARG register was completed using the following terms: Asthma OR Wheez* AND Emerg* OR acute OR status AND Discharge OR admi* OR hospit* AND Mag* OR magnesium sulfate OR MS. The symbol * is a qualifier that permits the search to include any use of the word irrespective of the suffix; for example Wheez* would identify articles using the following terms: "wheeze," "wheezing," "wheezes," and so on. Reference lists of all available primary studies and review articles were reviewed to identify potentially relevant citations. An advanced search of CCTR was completed using the terms: magnesium AND asthma. Inquiries were made regarding other published or unpublished studies known or supported by the authors of the included studies. Attempts were made to contact the primary investigators of included studies to obtain individual patient data; however, this was generally unsuccessful. Finally, personal contact with colleagues, collaborators, and other researchers working in the field of asthma was made to identify potentially relevant studies.

The search involved a 2-step process using 2 independent reviewers. First, from the title, abstract, or descrip-

tors, 2 reviewers (BR, JB) independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. Second, from the full text, using specific criteria, 2 reviewers (CB, GB) independently selected trials for inclusion in this review. Agreement was measured using κ statistics.³⁰ Disagreement was resolved by consensus or third-party adjudication (BR).

Assessment of the methodologic quality of included studies was conducted by 2 reviewers (JB, BR), working independently; both used 2 different methods of assessment. First, using the assessment of allocation concealment,³¹ all trials were scored and entered using the following principles:

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

In addition, each study was assessed using a 5-point scale developed by Jadad et al³² that has been shown to be valid and reliable. The scale examines issues of randomized, double-blind, withdrawals and dropouts, the methods of double-blinding, and randomization. Interrater reliability was again measured using κ statistics.³⁰

Data for the trials were extracted independently by 2 reviewers (BR, JB). Primary study authors were requested to confirm data extraction and provide additional clarification and information for the review. Unfortunately, most authors could not access their original data to perform supplemental analyses. In some cases, expansion of graphic representations of data was used to estimate missing data.

All trials were combined using the Review Manager (Update Software version 3.0; Update Software, Oxford, UK). For dichotomous variables, individual statistics were calculated as odds ratios (OR) with 95% confidence intervals (CIs). Pooling was completed using the DerSimonian and Laird method³³; a random effects model was used. The DerSimonian and Laird method³³ was also used to estimate the absolute risk reduction and the number needed to treat (NNT).³⁴

For continuous outcomes, individual statistics were calculated as weighted mean differences (WMD) and 95% CIs using a random effects model. The use of WMD is common in many systematic reviews and is the difference between the experimental and control group outcomes, when similar units of measure are used.³⁵ The weights given to each study in the pooled analysis are based on the inverse of the variance. Heterogeneity among pooled estimates was tested using the DerSimonian and Laird

method.³³ Sensitivity and subgroup analyses were performed to identify sources of heterogeneity when indicated.

Two specific subgroups were planned a priori. One was to compare adults with children. The other was to compare patients with severe asthma with those with less severe asthma. Sensitivity analyses were conducted on fixed versus random effects and methodologic quality (high versus low).

The debates about heterogeneity and the rationale for the use of fixed versus random effect models are beyond the scope of this article. Moreover, there is disagreement on how to summarize the results of studies, and whether they should be combined when substantial heterogeneity is identified. We have adopted the following approach in this review. First, we alert readers when there is substantial heterogeneity, and encourage cautious interpretation of the aggregated results. When heterogeneity is visually or statistically present, the pooled results should be interpreted cautiously. Second, we attempt to explore heterogeneity using subgroup and sensitivity analyses. Third, we use a random effects model when heterogeneity is present; this provides a more conservative estimation of the pooled estimate (and the CIs). Finally, we report the pooled estimate, in an attempt to provide an average measure of treatment effect.

RESULTS

The initial search yielded 90 references, of which 68 (76%) were identified as being original publications. Independent review of the abstracts and titles of these identified 8 potentially relevant studies. The agreement for relevance was very

good ($\kappa=0.76$). Additional references were sought from bibliographic searching of relevant articles and overviews (13), from author contact (5), and 1 through journal searching. A total of 27 studies were reviewed for inclusion; independent review of these potentially relevant articles resulted in 6 studies being included in this meta-analysis. The agreement for inclusion was excellent ($\kappa=1.0$). No relevant article was found from the journal search, bibliographic search, or recommendations from authors. An updated search was completed with the addition of one trial.³⁶ The search is considered updated to January 1999, and results are available from the authors on request.

The majority of studies were reported after 1989 (Table 1). Six were from centers in the United States; 1 was from India. Two studies were conducted in children^{36,37} and 5 in adults.³⁸⁻⁴² The populations varied from "all patients" with acute asthma ($n=2$), to only those with severe attacks ($n=5$). However, examination of the definitions used to designate the severe group (Table 2) reveals that patients had a combination of clinical findings, airflow measurements, and/or response to therapy that placed them in a more severe category. The admission rate was added to assist in the classification of severity, and does lend some support to the use of this method of clinical categorization of severity. For example, the severe subgroups have admission rates of more than 75%, whereas the mild-moderate subgroup has admission rates less than 30%. Only one study reported low admission rates (29% in placebo arm) among patients classified as "severe" by the author.⁴¹

Interventions used in the studies were well described and reproducible. Magnesium was administered "early" in the course of the ED treatment (Table 3). Two studies

Table 1.

Study and participant characteristics in 7 randomized trials of intravenous magnesium sulfate for acute asthma.

Study	Location, Year	Total Sample	Age Group	Age Range (y)	Sex (%F/%M)	Initial Pulmonary Function	
						PEFR Absolute (mean) L/min	PEFR % Predicted (mean)
Skobeloff et al ³⁸	US, 1988	38	Adults	18-70	74:26	150	NR
Green & Rothrock ³⁹	US, 1992	120	Adults	18-65	77:23	144	NR
Tiffany et al ⁴¹	US, 1993	48	Adults	18-60	56:44	131	NR
Bloch et al ⁴⁰	US, 1995	135	Adults	18-65	72:28	NR	34*
Silverman et al ⁴²	US, 1996	249	Adults	18-60	52:48	NR	23*
Devi et al ³⁶	India, 1997	47	Children	1-12	23:77	NR	27
Ciarallo et al ³⁷	US, 1996	31	Children	6-18	55:45	155	44

NR, Not reported.

*% Predicted FEV₁ provided rather than PEFR.

administered magnesium sulfate within 30 minutes,^{40,42} 3 were at approximately 1 hour,^{36,38,41} and 1 was unstated.³⁷ The route of administration was intravenous in all studies, and magnesium sulfate was administered as a bolus in all but one study where bolus ± a

continuous infusion was used.⁴¹ The dosage of intravenous magnesium sulfate delivery varied among studies; however, all studies used a placebo of similar appearance. The dose in adults ranged from 1.2 g to 2 g IV and was generally administered over 20 minutes.

Table 2.
Severity subgroups in systematic review of magnesium sulfate in acute asthma.

Study	Clinical Definition: Pulmonary Function Testing and Response to Therapy Criteria	Placebo Group Admission Rate (%)
Severe subgroup		
Bloch et al ⁴⁰ (severe subgroup only)	FEV ₁ <25% predicted following 1 β-agonist treatment	79
Ciarallo et al ³⁷	PEFR <60% predicted following 3 β-agonist treatments	100
Devi et al ³⁶	"Severe" asthma AND a poor response to initial therapy (no airflow measurements)	94
Skobeloff et al ³⁸	Initial PEFR <200 L/min AND failure to double PEFR after 2 β-agonists and >1 h of treatment	88
Silverman et al ⁴²	Initial FEV ₁ ≤30% predicted only	100
Mild-moderate severity		
Bloch et al ⁴⁰ (moderate subgroup only)	FEV ₁ 25%–75% predicted after 1 β-agonist treatment	24
Green & Rothrock ³⁹	"Unresponsive" to a single β-agonist treatment (no airflow measurements)	18
Discordant severity*		
Tiffany et al ⁴¹	Initial PEFR <200 L/min AND failure to double PEFR after 2 β-agonist treatments	29

*Discordant severity refers to discordance between authors' description of asthma severity and the overall admission rate in the placebo group.

Table 3.
Interventions and outcomes in 7 randomized trials of intravenous magnesium sulfate for acute asthma.

Study	Start of Magnesium Sulfate [†]	Magnesium Sulfate Regimen	Control Regimen	Corticosteroid Regimen	Reported Outcomes	Authors' Overall Conclusion	Jadad Quality Score
Skobeloff et al ³⁸	90 min	1.2-g loading dose over 20 min	50 mL saline solution	125 mg IV MP	Admissions, PFTs	Effective	5
Green & Rothrock ³⁹	60 min	2-g loading dose over 20 min	No placebo	125 mg IV MP	Admissions, PFTs	No effect	1
Tiffany et al ⁴¹	90 min	2-g loading dose ± 2-g/h infusion	Saline solution loading dose and infusion	125 mg IV MP	Admissions, PFTs	No effect	4
Bloch et al ⁴⁰	30 min	2-g loading dose over 20 min	50 mL saline solution	125 mg IV MP if initial FEV ₁ ≤40% or oral CS in the last 6 mo	Admissions, Borg Index	Overall: no effect; Severe group: effective	5
Silverman et al ⁴²	30 min	2-g loading dose over 20 min	50 mL saline solution	125 mg IV MP	Admissions, Borg Index, PFTs	Effective	4 [†]
Devi et al ³⁶	60 min	100 mg/kg loading dose over 35 min; maximum 2 g	30 mL saline solution	IV or PO corticosteroids (no dose provided)	Admissions, Pulmonary Index score, PFTs	Effective	4
Ciarallo et al ³⁷	After 3 ED β-antagonist treatments	25-mg/kg loading dose over 20 min; no maximum	"equi-volume" saline solution	2 mg/kg IV MP (75% of patients in study)	Admissions, PFTs	Effective	4

MP, Methylprednisolone; PFTs, pulmonary function test results reported; CS, corticosteroids.

[†]In minutes from time of arrival to ED.

[†]Jadad score results based on unpublished data.

In the pediatric studies, children received 25 mg/kg³⁷ or 100 mg/kg³⁶ (up to a maximum of 2 g) IV over 20 minutes.

Study cointerventions were reported in all studies. All patients received inhaled β -agonists; however, the agent, dose, and delivery methods varied. Methylxanthine administration was left to the discretion of the treating physician in all but 2 studies^{36,41} in which patients received intravenous aminophylline. Corticosteroids were routinely administered to all patients in 6 studies, and to those with the most severe asthma in the other.⁴⁰ Adult patients received 125 mg^{38,39,41,42} and children 2 mg/kg of intravenous methylprednisolone³⁷ or either intravenous or oral corticosteroids.³⁶ Ipratropium bromide was administered at the discretion of the treating physician in only one study.³⁹ Outcomes were determined at variable times and usually included admission to hospital/discharge assessment, and a variety of pulmonary function results (Table 3). Short-term follow-up was provided in 2 studies^{37,39} and at 1 week⁴⁰ to determine the rate of relapse to additional care. However, the variability of treatment approaches after discharge precluded pooling and comparisons. Side effects and vital signs were reported in sufficient detail to permit pooling.

Overall, the methodologic quality of the included studies was rated as high. Using the Cochrane concealment of allocation criteria, 5 studies were rated as having blinded allocation.^{36,37,40-42} It was unclear whether allocation was blinded in one study,³⁸ and in another study, allocation was clearly unblinded.³⁹ Agreement on concealment of allocation criteria was excellent ($\kappa=1.0$).

Many of the studies were double-blind ($\kappa=1.0$), placebo-controlled ($\kappa=1.0$), demonstrated an appreciation of the need for concealment of allocation, and reported a sufficient number of outcomes. Using the scale devised by Jadad et al,³² 5 studies were rated as "strong"^{36-8,40,41} and 1 was rated as "weak."³⁸ For one study, only partial Jadad scores could be calculated; a full manuscript was not available from one research group, so methodologic quality was verified through author contact and review of the methods section.⁴²

Results from this meta-analysis are reported by outcome. The main results are reported as overall effects of intravenous magnesium sulfate therapy versus placebo. In addition, the main subgroup based on asthma severity is also reported. All results are based on random effects models unless otherwise stated.

Sufficient studies were available in which hospital admission results were reported to permit pooling. No statistically significant difference was identified between

patients treated with magnesium sulfate or placebo with respect to hospital admission at the end of the study period (OR 0.40, 95% CI 0.15 to 1.07). However, this pooled result demonstrated significant heterogeneity ($\chi^2=19.53$; $df=5$; $P=.0015$). For patients within the severe asthma subgroup (Figure), hospital admissions in those treated with magnesium sulfate were lower than in those treated with placebo (OR 0.10, 95% CI 0.04 to 0.27). This pooled result did not demonstrate significant heterogeneity ($\chi^2=0.26$; $df=3$; $P=.97$). Using the risk difference, 8 patients (95% CI 5 to 12) would need to be treated with magnesium sulfate to prevent 1 hospital admission. There was no difference in hospitalization for the studies where participants had mild-moderate asthma (OR 1.36, 94% CI 0.72 to 2.55), and the results were also no longer heterogeneous ($P=.99$).

Sufficient results were also available in which pulmonary function results were reported to permit pooling. The PEF_R and % predicted FEV₁ were the most commonly reported pulmonary function tests, usually at the completion of the trial (or as close to 6 hours as possible). Patients receiving magnesium sulfate demonstrated nonsignificant improvements in PEF_R (WMD 29 L/min, 95% CI -3 to 62) and % predicted FEV₁ (WMD 4%, 95% CI -2 to 11) when all studies were pooled (Table 4). Statistically significant heterogeneity was identified for the results when all studies were pooled: PEF_R ($\chi^2=9.7$; $df=4$; $P=.05$) and % predicted FEV₁ ($\chi^2=7.47$; $df=2$; $P=.02$).

Improvement in lung function was more pronounced for those patients in the severe subgroup and heterogeneity was eliminated (Table 4). For example, in studies of severe acute asthma, PEF_R WMD improved by 52 L/min (95% CI 27 to 78), and these results were not heterogeneous. The % predicted FEV₁ also improved by 10% (95% CI 4 to 16) in the severe subgroup.

Vital signs were recorded and reported in many of the included studies; pooled results did not demonstrate statistical or clinical heterogeneity. These results indicate that heart rate (WMD 6 beats/min, 95% CI -2 to 13) and respiratory rates (WMD 0 breaths/min, 95% CI -3 to 3) did not change with intravenous magnesium sulfate treatment. Systolic blood pressure was slightly decreased (WMD -5 mm Hg, 95% CI -8 to -1). However, a change of this magnitude would not be considered clinically important. Overall, vital signs remained "stable" during the period immediately after administration of intravenous magnesium.

Monitoring of side effects was common in these studies, but few adverse events were reported. Magnesium sulfate appears to be a safe drug to administer to asth-

matic patients in the acute state. Four trials reported no major side effects; minor side effects (burning at intravenous site, flushing, fatigue) were reported by 58% of patients in one trial.⁴⁰ However, insufficient numbers of studies were available to provide meaningful sensitivity and subgroup comparisons or firm conclusions about side effects and adverse events.

For pooled admission rates, subgroup and sensitivity analyses were performed for the following categories: age (children versus adults), severity, methodologic quality, and statistical considerations. Both children (n=2; OR 0.09, 95% CI 0.01 to 0.56) and adults (n=3; OR 0.11, 95% CI 0.03 to 0.34) with severe asthma improved similarly. The results from the severe subgroups were reported above. When the study of lowest quality was eliminated,³⁹ the overall pooled admission rate remained statistically lower for magnesium sulfate than placebo (OR 0.29, 95% CI 0.1 to 0.94); however, the heterogeneity remained (P=.005). Using a fixed effects model, the overall admission rate was statistically significantly lower in the magnesium sulfate-treated

patients (0.54; 95% CI 0.33 to 0.87). This corresponds to an NNT of 15 (95% CI 9 to 63) to prevent one hospital admission.

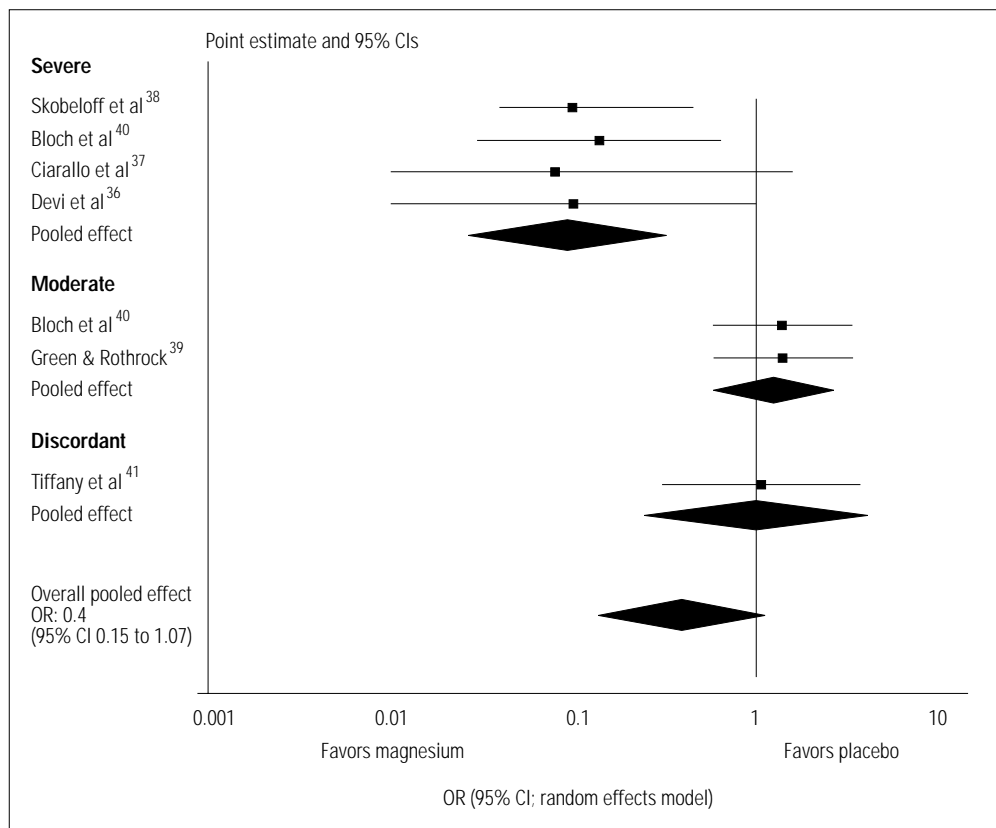
DISCUSSION

This systematic review examined the best available evidence for the use of intravenous magnesium sulfate in the ED management of acute asthma. Several important points arise from this meta-analysis. The pooled results failed to demonstrate statistically significant evidence of a beneficial effect of magnesium sulfate in terms of admission rates or pulmonary functions. Although the drug was well tolerated, the lack of effect argues against its indiscriminate use in the ED treatment of acute asthma.

Nevertheless, there is sufficient evidence to support its use in a subgroup of patients experiencing severe asthma attacks who appear to respond differently to the administration of magnesium. Patients who presented with severe asthma appeared to benefit from the use of

Figure.

Each study is represented by the point estimate for the outcome in question and by CIs on either side of that value. The vertical line corresponds to an odds ratio of 1.0; studies where the CI crosses the 1.0 line demonstrate no statistically significant difference between the groups (ie, those receiving magnesium sulfate versus those receiving placebo). Values to the left and not crossing the vertical line indicate a benefit of magnesium sulfate. The large horizontal diamonds in the figure correspond to the pooled results of the individual studies with narrower CIs.



intravenous magnesium sulfate, both in terms of pulmonary functions and admission rates. The NNT for this treatment in severe asthma is small (5 patients), further illustrating its effectiveness.

The clinical significance of the magnitude of the pulmonary function improvement is difficult to determine, since the minimally clinically important difference for lung function tests in severe acute asthma have not been determined. In chronic asthma, an improvement of 12% predicted has been quoted,¹² and for acute studies, some have suggested an increase in PEFR of as little as 30 L/min is clinically important.⁴¹ The improvement of approximately 10% predicted FEV₁ or 50 L/min PEFR demonstrated in this review represents what we believe may be important improvement in lung function, especially considering the severity at the start of therapy. Moreover, these lung function improvements correspond with important reductions in admissions.

In support of these subgroup findings, others have demonstrated magnesium sulfate to be of benefit in severe acute asthma. For example, Schiermeyer and Finkelstein⁴³ reported success with rapid magnesium sulfate infusion in children experiencing severe asthma and impending respiratory failure. Pabon et al⁴⁴ reported on the success of intravenous magnesium sulfate in children who had not responded to conventional treatment. Finally, high doses of intravenous magnesium sulfate have been used to treat ventilated patients to decrease peak airway pressure.⁴⁵ In summary, the use of magnesium sulfate in

patients with asthma appears justified on the basis of this meta-analysis and other research evidence.

One potential concern in this systematic review is the classification of the "severe" subgroup. It was based on primary authors' designation of "severe" (usually based on initial pulmonary function test results, and/or a failure to respond to therapy) and an examination of the admission rate in the placebo group by the review research team. Severe asthma was defined differently across studies, but included:

1. 25% to 30% predicted PEFR at presentation (adults)
2. Failure to respond to initial treatments (adults and children)
3. Failure to improve beyond 60% predicted after 1 hour of care (children)

In 4 studies, designation of severe by the author was concordant with high (>75%) admission rates. In 2 others, designation of mild-moderate was concordant with low admission rates (<25%). Only one study reported low admission rates (29% in placebo arm) among patients classified by the authors as "severe."⁴¹ We chose to classify the results from this study as "discordant" and present the data as a separate analyses. However, most emergency physicians will no doubt agree with the classification of severe assigned by the review team and used in this meta-analysis.

A consistent marker of the severity appears to be a failure to respond to initial β -agonist treatment (Table 2). For example, 4 studies in this review used this criterion to define severity.^{36-38,41} This observation leads to the recommendation that a failure to respond to initial β -agonist treatment may be an appropriate method of identifying those individuals who may benefit from magnesium sulfate treatment.⁴⁴

It is important to evaluate the validity of subgroup analyses in conjunction with these results. Guidelines for subgroup analyses have been published,⁴⁶ and should be considered within the context of this review. This meta-analysis used a subgroup based on baseline asthma severity that meets the above guidelines (ie, planned a priori and used in other airway reviews).⁴⁷ In addition, the differences in pooled estimates were large (OR 0.1 versus 1.36), demonstrated homogeneity across studies, and were physiologically reasonable. Furthermore, the subgroup results generated from both within⁴⁰ and between study comparisons were consistent.

Intravenous administration of magnesium sulfate was shown to be safe in those studies where vital signs and side effects were recorded. For example, magnesium treatment did not change pulse or respiratory rates; the

Table 4.

Pooled pulmonary function analyses for all studies and severe subgroup reporting results comparing magnesium sulfate with placebo in acute asthma.

Lung Function Result	All Studies WMD (95% CI)	Severe Subgroup* WMD (95% CI)
PEFR (L/min)	+29 L/min 95% CI -3 to 62 n=5 studies Heterogeneity† P=.05	+52 L/min 95% CI 27 to 78 n=3 studies No heterogeneity P=.62
% predicted FEV ₁	+4% predicted 95% CI -2 to 11 n=3 studies Heterogeneity P=.02	+10% predicted 95% CI 4 to 16 n=3 studies No heterogeneity P=.11

*See Table 2 for description of "severe" subgroups.

†All heterogeneity testing performed with DerSimonian and Laird method.³³ All results are reported using random effects modeling.

minor change in systolic blood pressure was clinically insignificant. Although this may seem counterintuitive, we suggest that the poor reliability and validity of respiratory rate measurement might explain these findings. For example, in one large ED study, almost all of the respiratory rates were recorded as 20/min.¹⁴ Caution is advised when interpreting the safety and adverse reaction data, since the total pooled sample size is insufficient to detect rare adverse events.

There is a possibility of publication bias in this meta-analysis.^{48,49} For example, by missing unpublished trials indicating negative results, we may be overestimating the effect of magnesium treatment. However, to reduce bias, a comprehensive and systematic search of the published and unpublished literature for potentially relevant studies was conducted.³¹ This was followed by attempts to contact corresponding and first authors. One unpublished trial was identified, and several trials indicating negative results were uncovered; however, we recognize that more of these types of trials may exist.

There is also a possibility of study selection bias.⁵⁰⁻⁵² However, we used 2 independent reviewers and are confident that the studies excluded were done so for consistent and appropriate reasons. Our search was comprehensive and has been updated, so it is unlikely that there are any published trials that were missed.

Recent publications have questioned the validity of results generated from meta-analyses. For example, LeLorier et al⁵³ concluded that agreement between large clinical trials and systematic reviews was low. However, careful examination of their results indicates systematic reviews provided conservative and surprisingly similar results to the mega-trials. Moreover, therapeutic mega-trials in most ED treatments are rare, expensive, and unlikely to be completed. Conversely, the alternative of individual clinicians approaching this problem will promote the practice variation in treatment we are currently experiencing. Thus, systematic reviews present an attractive alternative approach to treatment decisions and discordance can often be explained.⁵⁴

Finally, systematic reviews that pay close attention to methodologic quality^{31,50-52} have been shown to provide conservative and reasonable estimates of treatment effect.⁵⁵ Although they do not represent a panacea, they remain an important and growing component of evidence-based emergency medicine.^{56,57} They should be used in conjunction with clinical judgment and with patient preference in mind.⁵⁶⁻⁵⁸

Many questions regarding the treatment of acute asthma with magnesium sulfate remain unanswered. Most impor-

tantly, additional research is required to determine the optimal dose and duration of therapy. Additional studies are needed to confirm the subgroup findings from this review suggesting no effect of magnesium sulfate in mild and moderate asthma. In future studies, severity must be clearly defined and based on presenting pulmonary function results and response to initial β -agonist therapy whenever possible. Studies involving very young children need to be performed to determine the effect of magnesium sulfate treatment in this age group.

Further studies are required to examine the effect of magnesium sulfate based on the prior inhaled steroid use for patients presenting to the ED with acute asthma. The effect of treatment may differ based on inhaled steroid use,¹⁶ and the answer to this question remains unclear. Inhaled steroids are increasingly used, and the development of high-dose inhaled steroids with lower systemic activity suggests that this would be an important area for future research. Finally, acute asthma research must concentrate on well-defined outcomes that may lead to more informative reviews in the future. More specifically, criteria for discharge and reporting of lung function test data in a systematic fashion would assist in further work.

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A version of this review is published in an electronic format in the Cochrane Library (version 2, 1999).⁵⁹

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