

# Systematic Review Snapshot

## TAKE-HOME MESSAGE

Administration of intravenous magnesium sulfate may result in a modest reduction in hospital admissions among adult ED patients with acute asthma who have not responded to standard therapies.

## METHODS

### DATA SOURCES

Studies were obtained through the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, Allied and Complementary Medicine (AMED), PsycINFO, and by hand searching of respiratory journals and meeting abstracts through May 2014.

### STUDY SELECTION

Randomized controlled trials comparing any dose of intravenous magnesium sulfate with placebo among adult patients in the emergency department (ED) and with acute asthma exacerbations were reviewed by 3 authors, with a fourth author adjudicating disagreements. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was created to document the study selection process.

### DATA EXTRACTION AND SYNTHESIS

All 3 authors independently extracted outcome data, using a standardized collection form. Study quality was assessed by Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) considerations.<sup>1</sup> Risk of

## Does Intravenous Magnesium Reduce the Need for Hospital Admission Among Adult Patients With Acute Asthma Exacerbations?

### EBEM Commentators

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### Results

**Table.** Primary and secondary outcome measures for intravenous magnesium versus standard therapy.

| Outcome                        | Number of Patients (Studies) | OR or Mean Difference (MD) (95% CI) |
|--------------------------------|------------------------------|-------------------------------------|
| Hospital admission             | 1,769 (11)                   | OR 0.75 (0.60 to 0.92)              |
| Length of hospital stay (days) | 949 (3)                      | MD -0.03 (-0.33 to 0.27)            |
| PEF, L/min                     | 1,460 (8)                    | MD 17.4 (8.64 to 26.17)             |

PEF, Peak expiratory flow.

Eleven trials with a total of 1,769 participants provided sufficient information about the primary outcome (hospital admission). Seven of the 11 trials were randomized, double-blind, and placebo controlled; 2 were single-blind; 1 was unblinded with no placebo given; and for 1 trial, the study design was unclear.

Compared with controls, patients receiving a single infusion of either 1.2 or 2 g intravenous magnesium sulfate during 15 to 30 minutes experienced a small but significant reduction in rates of hospital admission (odds ratio [OR] 0.75), with minimal heterogeneity observed ( $I^2=28\%$ ). When the 3 studies at high or unclear risk of bias for blinding were removed, the pooled

effect for hospital admission was similar (OR 0.72; 95% confidence interval [CI] 0.57 to 0.91). There was no significant change in spirometric parameters (eg, peak expiratory flow) as well.

All studies included administration of inhaled  $\beta_2$ -agonists, and nearly all included administration of oxygen (9 of 11 studies) and corticosteroids (9 of 11 studies) before administration of magnesium, with a subset of patients also receiving inhaled ipratropium bromide (4 of 11 studies). There was no heterogeneity between studies in which ipratropium was and was not administered ( $I^2=0\%$ ). Inclusion criteria and the measures used to define an exacerbation

bias was determined according to the *Cochrane Handbook for Systematic Reviews of Interventions*, with planned sensitivity analysis for studies at high risk of bias for blinding. The authors used a fixed-effect model and performed a sensitivity analysis with random effects when heterogeneity was significant ( $I^2 > 30\%$ ).

were not consistent between studies; the majority of studies used various peak expiratory flow or forced expiratory volume in 1 second (FEV<sub>1</sub>) cutoffs. The authors could not fully establish how comedication or disease severity affected the treatment effect of magnesium. Adverse events were not consistently reported across studies and most commonly included headache, flushing, nausea, and hypotension, though the authors found no significant mean difference in systolic blood pressures between groups in the 4 studies (N=1,264; mean difference=0.08; 95% CI -1.89 to 2.05).

## Commentary

Asthma is a chronic disease afflicting approximately 300 million individuals worldwide,<sup>2</sup> and asthma exacerbations were responsible for more than 1.7 million ED visits in 2010 in the United States alone.<sup>3</sup> Standard therapies include nebulized  $\beta_2$ -agonists and corticosteroids, and often inhaled anticholinergics. Intravenous magnesium sulfate has been studied as an adjunct therapy, with previous systematic reviews

failing to demonstrate significant overall benefit in adults.<sup>4,5</sup>

The results of this systematic review indicate that intravenous magnesium sulfate, when administered in conjunction with standard therapies, may result in a modest reduction in hospital admission among adult patients with acute asthma exacerbations. This review was heavily weighted by Goodacre et al<sup>6</sup> (42.6% of the total patient population), who conducted a large, randomized, double-blind, placebo-controlled trial that showed a benefit for intravenous magnesium sulfate on rates of hospital admission (OR 0.70; 95% CI 0.50 to 0.97) when used in conjunction with oxygen,  $\beta_2$ -agonists, corticosteroids, and anticholinergics. Differences in how studies categorized disease severity made it difficult to draw conclusions about whether magnesium was more effective in severe asthma compared with moderate asthma, something indicated in subgroup analysis in the previous Cochrane review.<sup>5</sup>

Magnesium is thought to be involved in a number of important cellular processes, including inhibition of calcium influx into respiratory smooth muscle and modulation of acetylcholine release from cholinergic nerve terminals.<sup>7</sup> It is inexpensive, and life-threatening adverse events are rare.<sup>8</sup> Coupled with the moderately persuasive findings of this review, it is reasonable to offer a trial of intravenous magnesium for adult patients with acute asthma who are not responding to standard therapies.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2014;(5):CD010909. <http://dx.doi.org/10.1002/14651858.CD010909.pub2>.

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Michael Brown, MD, MSc, Alan Jones, MD, and David Newman, MD, serve as editors of the SRS series.