

Intravenous Magnesium for Acute Asthma Exacerbations in Children: To Mag or Not to Mag



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Asthma is the most common chronic illness in the pediatric population, affecting approximately 7 million children in the United States.¹ Acute asthma exacerbations are a leading cause of health care utilization, accounting for 750,000 emergency department (ED) visits, 200,000 hospitalizations, and \$50 billion in health care costs annually.² First-line therapy for acute asthma exacerbations includes bronchodilators and systemic corticosteroids. Second-line therapies are considered for exacerbations refractory to initial therapies and are used more variably in terms of timing, method, and dose of administration. Intravenous magnesium (IV-Mg) is a second-line therapy frequently used for the treatment of refractory moderate and severe acute asthma exacerbations. Early studies suggested promise of IV-Mg in improving lung function and reducing hospitalizations for children with acute asthma exacerbations in the ED.³⁻⁵ However, recent studies have highlighted the variability in use of IV-Mg and questioned its efficacy in improving clinical outcomes.^{6,7}

Ciarallo et al³ first evaluated the efficacy of IV-Mg in moderate and severe acute asthma exacerbations by conducting a trial of 31 children with refractory exacerbations who were randomized to receive IV-Mg (25 mg/kg, maximum 2 g) versus placebo. The authors demonstrated improved lung function and decreased hospital admission in the IV-Mg treatment group. The authors subsequently conducted a trial in 30 children evaluating a higher dose of IV-Mg (40 mg/kg, maximum 2 g) and demonstrated similar findings.⁴ Although these studies showed benefit of IV-Mg, Scarfone et al⁶ conducted a trial of 54 children randomized to a higher dose of IV-Mg (75 mg/kg, maximum 2.5 g) versus placebo, and found no difference in clinical severity or hospitalization rates between groups. Authors of a Cochrane review included the 3 aforementioned trials in their analysis and found a reduction in the odds of hospitalization by 68% (odds ratio, 0.32; 95% CI, 0.14-0.75) in children with moderate and severe asthma exacerbations treated with IV-Mg compared with placebo.⁵ However, the authors stated that the evidence for this finding was weak due to small numbers (115 children total), heterogeneity of studies, and inability to perform a subgroup

analysis by severity. Regardless, based on the suggested benefit and lack of serious adverse events, IV-Mg has been used with increased frequency for the treatment of children with moderate and severe acute asthma exacerbations.⁸

Recent studies have provided insight into the use of IV-Mg in current clinical practice. A multicenter retrospective study of 7 pediatric EDs demonstrated substantial variability among EDs in terms of characteristics of IV-Mg administration (eg, timing and dosing).⁹ The median time of administration was 154 minutes (late in the ED course), and almost 90% of patients who received IV-Mg were hospitalized, thus questioning the current clinical role of IV-Mg in children with acute asthma exacerbations. Another study of 35 children's hospitals demonstrated that, despite increased use of IV-Mg, there has been no improvement in the rate of hospital and intensive care unit admissions for pediatric asthma exacerbations in over a decade.⁸ In addition, a recent secondary analysis of a prospective, multicenter trial of nebulized magnesium found that children who received IV-Mg had almost 10 times greater odds of being hospitalized compared with those who did not receive IV-Mg (odds ratio, 9.76; 95% CI, 4.58-20.77), even after adjustments to account for patient-level characteristics, including clinical severity.⁷

Given that existing literature regarding the efficacy of IV-Mg in children with acute asthma exacerbations is inconclusive, further exploration is warranted. In this issue, Arnold et al¹⁰ report their secondary analysis of data from a prospective observational study of children with moderate and severe acute asthma exacerbations. The authors found that receipt of IV-Mg was associated with increased exacerbation severity as measured by the Acute Asthma Intensity Research Score (AAIRS), a previously validated clinical asthma severity score. Their findings question the utility of IV-Mg for the treatment of pediatric acute asthma.

The parent study included children aged 5 to 17 years with moderate and severe acute asthma exacerbations who received systemic corticosteroids and inhaled albuterol, with consideration for IV-Mg (75 mg/kg, maximum 2.5 g) in those with insufficient response after 20 minutes. For their analysis, the authors used propensity score-based models to test the association between receipt of IV-Mg and clinical outcomes. Receipt of IV-Mg was associated with a 2-hour increase in the AAIRS (B-coefficient, 0.98; 95% CI, 0.20-1.77), 5.8-fold (95% CI, 2.8-11.9) greater odds of hospitalization, and no difference (hazard ratio, 1.2; 95% CI, 0.8-1.8) in time to every 4-hour inhaled albuterol among hospitalized patients. These findings are consistent with recent studies demonstrating lack of clinical benefit of IV-Mg for children with moderate and severe acute asthma exacerbations.^{7,8}

This article augments current evidence by using a robust propensity score model and a large, prospectively derived cohort to determine the efficacy of IV-Mg for children with moderate

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and severe acute asthma exacerbations. As the authors note, a challenge with studying IV-Mg is confounding by indication; reasons for administering IV-Mg may also influence outcomes of interest. For instance, children with more severe exacerbations are more likely to be admitted, regardless of receipt of IV-Mg. Propensity score modeling accounts for the differences in measured variables between treatment groups and reduces the effects of confounding. However, propensity score modeling cannot account for the differences in possible unmeasured variables between treatment groups, which is a major limitation of studies of IV-Mg.

Currently, there is no consensus on a clinically meaningful outcome to assess the efficacy of IV-Mg in children with acute asthma. Arnold et al¹⁰ use change in asthma severity as measured by the AAIRS as their primary outcome. The authors state that administration of IV-Mg was associated with increased exacerbation severity based on the 2-hour change in AAIRS. However, the difference in 2-hour change in AAIRS was 1.0, the clinical significance of which is unknown. Use of a clinical severity score as an outcome is challenging, because multiple asthma scores exist, and no one score is reported consistently in the literature. Numerous studies use hospitalization as a primary outcome to assess the efficacy of IV-Mg. However, the decision to admit is influenced by many variables, including acute exacerbation severity, institutional policy, provider risk-tolerance, and access to outpatient follow-up. Notably, Arnold et al¹⁰ evaluated time to every 4-hour inhaled albuterol in children who were hospitalized. This outcome provides an objective measure of symptom resolution and need for hospital admission and should be considered in future trials of acute asthma exacerbations.

Existing studies of IV-Mg have also widely differed in patient population, and time of administration and dose of IV-Mg studied. Similar to previous studies, Arnold et al¹⁰ evaluate IV-Mg for the treatment of children with moderate and severe acute asthma exacerbations refractory to initial therapies. However, it is possible that early administration of IV-Mg, before or during initial therapies, might demonstrate more beneficial results.⁹ In addition, Arnold et al¹⁰ use a dose of 75 mg/kg (maximum 2.5 g) of IV-Mg in accordance with the institutional clinical pathway; previous studies have evaluated doses from 25 to 75 mg/kg.^{3,4,6,7} The lack of consensus on the appropriate

administration of IV-Mg contributes to the substantial variability among studies, which in turn inhibits meaningful conclusions on the efficacy of IV-Mg for children with acute asthma exacerbations.

Overall, Arnold et al¹⁰ add to the growing literature questioning the efficacy of IV-Mg for children with moderate and severe acute asthma exacerbations. Clinicians should recognize the potential lack of benefit and limitations of current evidence when considering whether or not to administer IV-Mg. A future trial that prospectively assesses the efficacy and safety of IV-Mg is needed. Strong consideration should be given to early administration, objective measurement of asthma severity, and a clinically meaningful outcome.

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