

High-Dose Magnesium Infusions for Acute Severe Asthma in Children: If a Little Is Good, Is More Even Better?*

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Compared with the millions of acute asthma exacerbations occurring in children each year, severe, potentially life-threatening exacerbations are relatively rare, accounting for only about 10,000 annual admissions to an ICU in the United States (1, 2). But in a PICU, where all of the illnesses are relatively rare, severe asthma exacerbations are the most common admission diagnoses (1, 2). There are few evidence-based treatment strategies, and as a result, after first-line therapies of albuterol and corticosteroids, treatment for severe asthma is highly variable (1–3). In refractory exacerbations, providers will sometimes use the “kitchen sink” approach, in which multiple different treatments are given all at once in an effort to prevent further deterioration of a critically ill child.

Magnesium is a second-line therapy that is frequently used for acute asthma in children. Magnesium is inexpensive and generally safe and effective at typical doses (4–6). It is usually given IV as a bolus (5, 6), although some authors have investigated its use via inhalation (7). Magnesium is thought to treat asthma by at least two different mechanisms (4, 5). First, it is a smooth muscle relaxant that bronchodilates via antagonism of calcium channels of the bronchial smooth muscles (4). Second, magnesium is thought to inhibit degranulation of mast cells; and so, it may improve acute asthma via reduction of both histamine and prostaglandin release (4). However, magnesium is a nonselective muscle relaxant, and at high doses, it has potentially significant side effects as a result of relaxing smooth muscles throughout the body. These include flushing, dizziness, muscle weakness, and hypotension.

Trendelenburg (yes, that Trendelenburg) was the first to report magnesium's bronchodilator effects in 1912 (albeit in cows) (8). By the 1930s, Rosello and Pla (9) were among the first to report the use of magnesium for the treatment of asthma in

humans. More recently, there have been several small, randomized, placebo-controlled trials of the use of IV magnesium for the treatment of severe asthma. A metaanalysis of five of these trials found that the addition of IV magnesium to conventional first-line therapy in the emergency department (ED) significantly reduced hospitalization for acute asthma (odds ratio, 0.29; 95% CI, 0.14–0.59) and resulted in significantly improved pulmonary function and clinical asthma score (7). Taken together, these studies suggest that magnesium may be a useful adjunct for the treatment of refractory acute asthma in children.

In their article in this issue of *Pediatric Critical Care*, Irazuzta et al (10) conducted a prospective, randomized, open-label study to determine whether high-dose magnesium infusions might be effective in reducing hospitalizations during severe asthma exacerbations. The study builds upon the authors' previous work examining the feasibility and safety of high-dose magnesium infusions in the pediatric ICU (11). The investigators theorized that because repeated doses of magnesium are sometimes used in children with status asthmaticus, a higher dose, short-term infusion may be more effective than a single bolus given magnesium's rapid elimination by the kidneys.

Thirty-eight children presenting to the ED with severe asthma exacerbations were randomized to receive either a lower dose magnesium bolus (50 mg/kg) or a high-dose magnesium infusion (50 mg/kg/hr $\times$ 4 hr) (10). Children also received conventional first-line therapy with salbutamol nebulizers every 20 minutes and IV dexamethasone. The investigators found that children treated with high-dose magnesium infusions were significantly more likely to be discharged within 24 hours and had shorter lengths of stay and lower hospital costs per patient. There were no reported adverse events with the use of high-dose magnesium infusions in this small cohort (10).

The study by Irazuzta et al (10) has several strengths. Conducting clinical trials in children with acute asthma is challenging, and this study is well designed and well conducted. Although the numbers are relatively small, the percent enrolled was high. The authors used a clinical asthma score to benchmark severity of illness on presentation, and this score had a strong correlation between the evaluators. Although the study was open-label, the primary outcome, discharge home at 24 hours, was determined by a physician blinded to the medication received.

There are, however, several limitations of the study (10). As the authors acknowledge, this was a single-center study with a low number of study patients. Because of the relatively rare occurrence of this illness in the overall population, this is a common limitation of studies in acute asthma in children. The main physiologic rationale for the utility of a magnesium infusion is the high rate of the drug's elimination. Therefore, the collection

*See also p. e29.

Key Words: asthma; magnesium; pediatric; status asthmaticus

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of magnesium levels would have been a nice addition to this study, although this may not have been possible given the setting. In addition, although asthma scores were used to benchmark illness severity at admission, scores were not tracked throughout the course of the exacerbation, which may have provided some useful insight into patients' rates of improvement. Also, interestingly, none of the patients in this cohort were obese, raising questions about its generalizability because typically more than one in five children with acute asthma are also obese (12).

So should high-dose magnesium infusions be used in children with refractory and severe asthma exacerbations? There is mounting evidence that magnesium is a useful adjunct, particularly in the ED setting and early in the disease course. However, thus far, Dr. Irazuzta et al (10) are the only ones who have published on the use of higher dose, short-term magnesium infusions in this population. We remain cautious of the "if a little is good, more is even better" approach to asthma therapy. Nonetheless, for magnesium, the more rapid elimination suggests that an infusion may have a role in refractory exacerbations and may be of particular use in the ED or the ICU. In addition, because magnesium is comparatively easy to give, has a relatively good side effect profile, and is inexpensive, it may be useful in areas with limited resources. Much more research is needed into the safety and efficacy of this therapy before we can recommend its widespread use. But based on this small study, it seems that higher dose, short-term infusions may be a useful adjunct to conventional first-line therapy for acute asthma.

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Children Are Not Just Little Adults...*

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Where should critically ill children be cared for to achieve the best outcomes? Naturally, we as pediatric intensivists believe that the answer is "in a PICU". Although some may call us biased, this theory is not an unreasonable one. Children often have different diseases, developmental issues, and possibly differential responses to therapies when compared with adult patients; it would make sense that pediatric specialists would have a certain expertise and skillset

that nonpediatric physicians may lack. Furthermore, having pediatric-specific support staff and equipment may facilitate more rapid and effective implementation of critical care. Such rationale has led to recommendations for regionalizing services for critically ill and injured children although the evidence supporting these recommendations has been moderate, at best (1, 2).

In this issue of *Pediatric Critical Care Medicine*, Peltoniemi et al (3) present additional data in favor of centralization of pediatric critical care. In this study, the authors analyzed 2 years of data from 29 ICUs in Finland, comparing the characteristics and outcomes of children admitted to either 1) one of three PICUs or 2) one of the adult ICUs, based on either a university hospital or a nonacademic central hospital. Among this cohort, children admitted to an adult ICU had a shorter ICU length of stay than those admitted to a PICU. However, on multivariate analysis, the risk of mortality associated with admission to an adult ICU was almost four times that of an admission to a PICU. Although the study captures national data and the strength of association was quite strong, there are several issues worth considering when interpreting the findings.

*See also p. e43.

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