

The effectiveness of magnesium sulfate for status asthmaticus outside the intensive care setting

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Abstract

Aim: Magnesium is an adjunctive therapy used in patients with status asthmaticus who do not respond to conventional therapy. The optimal time from initiation of therapy, to determination of response and administration of magnesium has not yet been resolved. Our objective was to determine if magnesium administered in the non-intensive care setting can decrease duration of continuous albuterol and hospital length of stay.

Methods: We performed a retrospective cohort analysis of children ages 2-18 years admitted to the pediatric unit on continuous albuterol between January 2014 and December 2015 in a tertiary care children's hospital. Cohorts were matched on respiratory assessment score (RAS) obtained at a similar duration of albuterol therapy and evaluated for the total duration of continuous albuterol, length of stay (LOS), and adverse events.

Results: Thirty-three patients who received magnesium were matched to 33 patients with the same RAS at a similar duration of continuous albuterol therapy who did not receive magnesium. Those who received magnesium had longer duration on continuous albuterol (34 vs 18 h; $P = 0.001$; 95% confidence interval [CI] 4-20; effect size 0.41) and longer LOS (72 vs 49 h; $P = 0.037$; 95% confidence interval [CI] 1-33; effect size 0.26) than those who did not receive magnesium.

Conclusion: Children requiring continuous albuterol for status asthmaticus can be administered magnesium sulfate outside the PICU with a low incidence of adverse events; however, among a RAS matched cohort, those who received magnesium did not experience shorter time on continuous albuterol, or hospital length of stay.

KEYWORDS

asthma, magnesium sulfate, status asthmaticus

Abbreviations: EHR, electronic health record; ED, emergency department; HR, heart rate; ICU, intensive care unit; I:E time, inspiratory expiratory time; LOS, length of stay; PICU, pediatric intensive care unit; RAS, respiratory assessment score; RR, respiratory rate; (Q2), every 2 h.

Presentation of Information: Included data has previously been presented in poster form at the New Jersey chapter of the American Academy of Pediatrics annual conference (Somerset, NJ; May 11, 2016), the American Academy of Pediatrics national conference (San Francisco, CA; Oct 11, 2016), and the Camden scholars' forum (Camden, NJ; April 17, 2017).

1 | INTRODUCTION

Inhaled bronchodilator therapy in combination with systemic corticosteroids is the standard therapy for status asthmaticus due to their demonstrated safety and efficacy.¹⁻³ However, children who fail to improve on this regimen tend to receive a variety of treatments, most of which are not evidence based.⁴ Magnesium sulfate is one such adjunctive therapy recommended by the National Heart, Lung, and Blood Institute in patients with severe asthma exacerbations after 1 h

of therapy to avoid intubation.¹ When added to standard therapy in the emergency department (ED), magnesium sulfate reduces persistent bronchoconstriction, and decreases hospitalization rates.⁵⁻⁷ Traditionally, children with status asthmaticus who require continuous albuterol therapy after disposition from the ED have been cared for in the pediatric intensive care unit (PICU) or intermediate care setting.⁸

Emerging evidence suggests that continuous albuterol is safe to administer outside the intensive care unit (ICU)^{2,9,10}; however, no studies to date have evaluated the use of adjunctive therapies outside the ED or the intensive care setting. We sought to assess the efficacy of magnesium sulfate administration among pediatric patients admitted to the general medical floor or intermediate care unit who required continuous albuterol for at least 6 h after having already received three doses of albuterol plus ipratropium and systemic corticosteroids. Our hypothesis was that magnesium sulfate administration would decrease both time on continuous albuterol and hospital length of stay, regardless of asthma severity as indicated by the respiratory assessment score (RAS).

2 | METHODS

This is a retrospective cohort study performed at an urban, tertiary care children's hospital in Camden, NJ. Children age 2-18 years admitted to the general pediatric floor or pediatric intermediate care unit (care provided by the general pediatric team) between January 1, 2014 and December 31, 2015 on continuous albuterol were screened for inclusion.

A list of patients with an order for continuous albuterol during their hospitalization was generated through the electronic health record (EHR; Epic Systems Corporation, Verona, WI). Patients were manually screened through review of the EHR for inclusion criteria: 1) age 2-18 years; 2) diagnosis of asthma exacerbation or status asthmaticus; 3) received three doses of albuterol plus ipratropium and a dose of corticosteroids in the Cooper University Hospital emergency department; 4) received continuous albuterol for at least 6 h, and 5) initially admitted to the general medical floor or intermediate care unit. Patients were excluded if any of the following were present: 1) concomitant diagnosis of bronchiolitis, pneumonia, or other acute lung pathology and 2) transferred from an outside facility. Prematurity was not considered an exclusion criterion. The study was approved by the Institutional Review Board at Cooper University Hospital in Camden, NJ (IRB 15-098EX).

For patients who received magnesium, we calculated the time (in hours) from initiation of continuous albuterol to administration of magnesium and then determined the RAS prior to the treatment (as documented in the EHR). For those who did not receive magnesium, we calculated the time (in hours) from the start of continuous albuterol until discontinuation and reviewed all documented RAS while on the therapy. Time of initiation of albuterol, discontinuation of albuterol, and administration of magnesium were determined by review of the medication administration record in the EHR. Patients treated with magnesium were matched to a patient who did not receive magnesium

when they had an identical RAS documented at a similar duration of time on continuous albuterol. In the event of having multiple patients with the same duration of continuous albuterol and respiratory assessment scores, patients were then matched on age.

Patient demographics, prior asthma history, prescribed home medications, vital signs, ED examination, time on continuous albuterol, length of time from magnesium administration to discontinuation of continuous albuterol, need for transfer to PICU, need for increased respiratory support, length of stay (LOS), rate of 7 day return to the ED, and rate of 30 day hospital re-admission were compared between the group that received magnesium and the group that did not receive magnesium. Initial RAS on presentation to the hospital was calculated using vital signs and the first documented examination (respiratory rate, ratio of inspiratory to expiratory time, presence of retractions, presence of wheezing, SpO₂, work of breathing, and activity level) in the ED. All other RAS were recorded as documented in the EHR by the team caring for the patient (protocol for documentation as described below).¹¹

All patients were administered three consecutive doses of albuterol 2.5 mg plus ipratropium 0.5 mg nebulizations and steroid therapy in the ED; the steroid regimen consisted of prednisolone 2 mg/kg oral loading dose with a maximum dose of 60 mg, prednisone 60 mg oral loading dose, or methylprednisolone 1 mg/kg IV loading dose with a maximum dose 120 mg.

The hospital protocol for management of status asthmaticus is to start continuous albuterol nebulization at a dose of 0.5 mg/kg/h rounded to the nearest 5 mg/h (maximum dose 15 mg/h) and to continue steroid therapy with prednisolone 1 mg/kg oral (maximum 30 mg/dose) twice daily, prednisone 1 mg/kg oral (maximum 30 mg/dose), or methylprednisolone 0.5 mg/kg IV (maximum dose 15 mg/dose) four times per day for 5 days total duration. When a RAS less than or equal to four is achieved, albuterol HFA with a spacer is started every 2 h at a dose of four puffs of 90 mcg/actuation for children less than 10 kg or six puffs of 90 mcg/actuation for children greater than 10 kg with sequential spacing of albuterol treatments in 1 h increments for each RAS less than or equal to 4. RAS are documented by the nurse, physician, or respiratory therapist after each clinical assessment performed at 1-4 h intervals, immediately before albuterol administration. Patients are discharged after two administrations of every 4 h albuterol treatments. Duration of continuous albuterol (in hours) was determined through review of the medication administration record as documented in the EHR and LOS was calculated from EHR nursing documentation of reception of the patient on the pediatric floor until a physician order for discharge was placed.

Patients in the magnesium cohort were given one or more doses of magnesium sulfate ranging from 25 to 75 mg/kg/dose (standard dose was 50 mg/kg/dose) with a maximum of 2000 mg/dose administered over 60 min at the discretion of the physician caring for the patient. While there are no institutional guidelines for the use of magnesium sulfate, usual indications for administration include perceived high disease severity, and disease deemed refractory to current therapy. The safety of magnesium was determined by evidence of documented hypotension, respiratory depression, or arrhythmia.¹² Shapiro-Wilk

Test of Normality indicated the data was non-parametric therefore the Mann-Whitney *U* test with the Hodges Lehman statistic was used to compare ranks and estimate confidence intervals. Wilcoxon Signed Rank Test and McNemar Test were used to compare data between study groups. All tests were two sided with values $P < 0.05$ considered statistically significant. Data analysis was completed with SPSS Statistics 22.0 (International Business Machines Corporation, New York, NY).

3 | RESULTS

Five hundred and sixteen patients were identified as having an order for continuous albuterol therapy during the study period. Of 142 patients who met inclusion criteria 33 received at least one administration of magnesium sulfate and 33 patients who did not receive magnesium were selected as a matched cohort (Figure 1).

Baseline characteristics were similar between the groups except for patient age and heart rate on presentation the emergency department (Table 1). Illness severity on presentation to the pediatric floor was similar between groups (median RAS 4.3 vs 4.3; $P = 0.943$) and remained comparable with mean RAS (4.5 vs 4.4; $P = 0.18$) documented at a similar duration of continuous albuterol therapy (7 h vs 8 h; $P = 0.01$). Those who received magnesium had longer median duration on continuous albuterol (34 vs 18 h; $P = 0.001$; 95% confidence interval [CI] 4-20; effect size 0.41) and longer median

LOS (72 h vs 49 h; $P = 0.037$; 95% confidence interval [CI] 1-33; effect size 0.26) when compared to those who did not receive magnesium.

The median time to administration of magnesium was 8 h (IQR 5, 16) after initiation of continuous albuterol and the median duration of continuous albuterol after first magnesium administration was 19 h (IQR 10, 32).

There were no adverse events (hypotension, respiratory depression, or arrhythmia) attributed to magnesium administration in any of the 33 patients; both cohorts had patients who experienced hypotension (3 vs 3; $P = 1.00$) and respiratory depression (8 vs 3; $P = 0.227$) ranging from the time of hospital admission to more than 100 h after admission, all of which resolved without significant intervention. However, 9 (27%) patients who received magnesium sulfate did require transfer to the PICU versus only 2 (6%) in the cohort who did not receive magnesium therapy ($P = 0.065$).

4 | DISCUSSION

Prior studies have found that patients who present with moderate to severe asthma exacerbations and are treated with β -agonists and corticosteroids alone typically show incomplete response to therapy and frequently require hospitalization.⁸ A recent study by Kenyon et al² examined pediatric patients on continuous albuterol therapy admitted to the pediatric medical floor or pediatric intermediate care unit and showed a median duration of therapy of 14.4 h with an

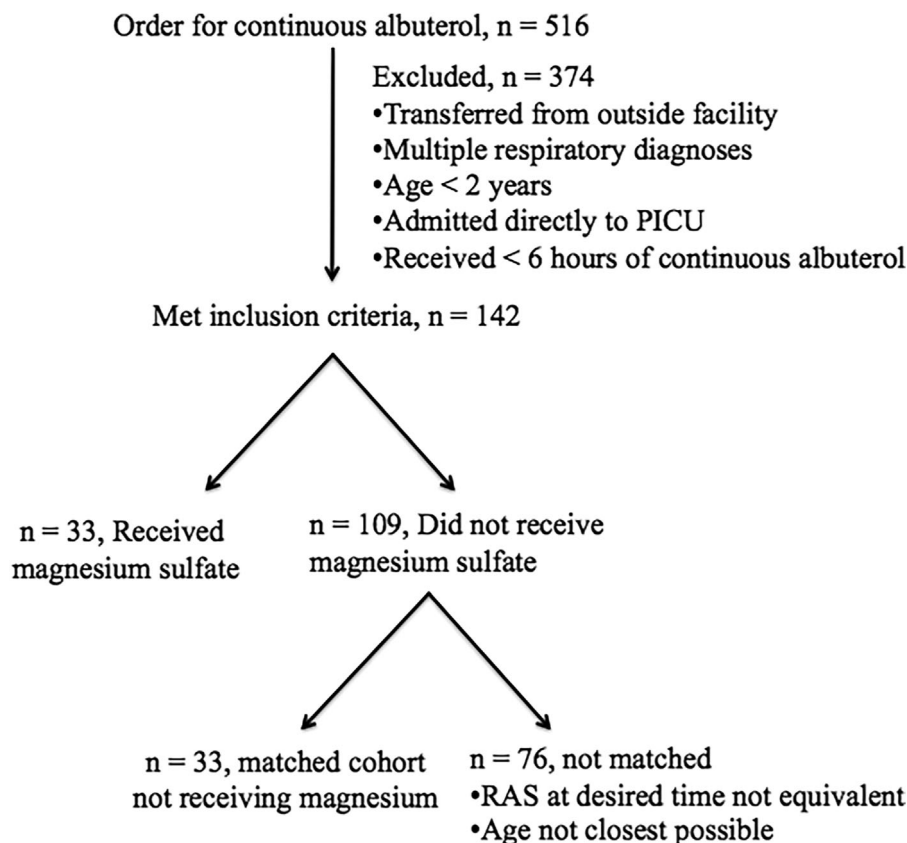


FIGURE 1 Cohort selection

TABLE 1 Demographics

Factors	Entire cohort n = 66	No magnesium administered n = 33	Magnesium administered n = 33	P-value
Gender (%)				0.508
Male	45 (68)	21 (63)	24 (72)	
Female	21 (31)	12 (36)	9 (27)	
Age (%)				0.045
2-5 y	22 (33)	15 (46)	7 (21)	
6-10 y	29 (43)	12 (36)	17 (51)	
>10 y	15 (22)	6 (18)	9 (27)	
Race (%)				0.079
White	9 (14)	7 (21)	2 (6)	
African American	31 (47)	15 (45)	16 (48)	
Hispanic	25 (38)	11 (33)	14 (42)	
Other	1 (2)	0 (0)	1 (3)	
Home controller prescribed (%)	44 (66)	20 (65)	23 (74)	0.629
Previous year ED (%)	37 (56)	15 (46)	22 (66)	0.143
Previous year hosp (%)	26 (39)	10 (30)	16 (49)	0.180
Prior ICU admission (%)	12 (18)	4 (13)	8 (26)	0.344
ED factors (SD)				
Mean HR	128 (21)	134 (18)	123 (23)	0.039
Mean RR	34 (14)	37 (15)	31 (12)	0.073
Mean SaO ₂	93 (9)	93 (6)	93 (12)	0.909
Mean initial RAS	4 (2)	5 (2)	4 (1)	0.053
Magnesium administered (%)	8 (12)	4 (12)	4 (12)	1.000
Terbutaline administered (%)	2 (3)	0 (0)	2 (6)	
Pediatric floor factors				
Mean RAS on pediatric floor (SD)	4 (2)	4 (2)	4 (2)	0.943
Mean RAS 6 h after initiation of therapy (SD)	4 (2)	4 (2)	4 (2)	0.147
Number transferred to PICU (%)	11 (17)	2 (6)	9 (27)	0.065
Need for respiratory support (VPT, CPAP, BiPap) (%)	10 (15)	3 (9)	7 (21)	0.344
Hypotension ^a (%)	6 (9)	3 (9)	3 (9)	1.000
Respiratory depression ^b (%)	11 (17)	3 (9)	8 (25)	0.227
Discharge factors (%)				
Return to ED for asthma within 7 days of discharge	3 (5)	1 (3)	2 (6)	1.000
Re-admission for asthma within 30 days of discharge	2 (3)	2 (6)	0 (0)	

^aSBP < 70 + (age in years × 2) for children 2-10 years and SBP < 90 mm Hg for children > 10 years.¹¹

^bRR < 22 for 2-5 years, RR < 18 for 5-10 years, and RR < 12 for > 10 years.¹¹

Shaded area represents "N/A" (numbers that cannot be calculated due to n = 0)

average length of stay of 57.0 h; 26% were on continuous albuterol more than 24 h with 10% being transferred to the PICU. In our cohort of 33 patients who did not receive magnesium sulfate, our median time on continuous albuterol was 18 h and median length of stay 49 h with

30% on continuous albuterol more than 24 h and 6% being transferred to the PICU.

Magnesium sulfate has demonstrated superiority over other adjunctive therapies in the emergency department and has consistently

demonstrated benefit over placebo^{5-7,13,14}; however, for patients not admitted to the ICU who require continuous albuterol therapy there currently is insufficient evidence to support administration of any adjunctive therapy. When used in the emergency department, patients who receive intravenous magnesium experience, approximately 85% reduction in risk of persistent bronchoconstriction, and demonstrate an objective improvement in clinical response scores.⁵ Magnesium, when compared with other therapies, has the advantage of widespread availability, low cost, and minimal adverse effects.¹³ The only study to date that has evaluated the use of magnesium sulfate in asthmatic patients on the pediatric ward also included those in the intensive care unit and did not demonstrate shorter duration of continuous albuterol or LOS in those who received intravenous magnesium sulfate.¹⁰ Our study expands on these findings in that those who received magnesium did not have shorter length of continuous albuterol therapy or shorter length of stay than those who had a similar respiratory assessment score but did not receive magnesium. While this may represent a selection bias in that patients who require longer courses of continuous albuterol may be more likely to be given magnesium at our hospital, matching patients on respiratory assessment score at the same time point reduces this bias potential by controlling for variables associated with its administration. Namely, matching on RAS allowed us to control for disease severity while matching at a similar time point allowed us to compare those deemed to have a refractory disease course.

While the respiratory assessment score has not been validated in the management of pediatric asthma, its component parts are similar to previously published asthma scoring systems. Three such systems have been validated for use in children that share similar clinical criteria.¹⁵⁻¹⁷ The Pediatric Respiratory Assessment Measure has been validated for children 3 to 17 years of age and calculates a score from 0 to 12 by evaluating oxygen saturation, presence of retractions, air entry, and wheezing quality/quantity.¹⁵ The Pediatric Asthma Severity Score has been validated for children 1 to 18 years of age and calculates a score from 0 to 10 by evaluating air entry, work of breathing, prolongation of expiration, wheezing quality/quantity, presence of tachypnea, and mental status.¹⁶ And the Acute Asthma Intensity Research Score has been validated for children 5 to 17 years of age and calculates a score from 0 to 16 by evaluating air entry, wheezing quality/quantity, oxygen saturation, prolongation of expiration, and presence of retractions.¹⁷

As magnesium levels were not routinely measured for the study patients and dosing was not standardized, it is possible that inadequate doses of magnesium sulfate were administered in an attempt to achieve therapeutic benefit. While the mechanism by which magnesium sulfate relieves bronchoconstriction in asthmatic patients is still largely unknown; several different mechanisms have been proposed. The predominant theories include: 1) inhibition of cellular uptake of calcium across smooth muscle membranes leading to bronchial smooth muscle relaxation; 2) inhibition of degranulation of mast cells thus reducing inflammatory mediators such as histamine, thromboxanes, and leukotrienes; 3) inhibition of acetylcholine release at motor nerve terminals depressing the excitability of muscle fiber membranes; and 4) stimulation of nitric oxide and prostacyclin synthesis.^{5,18-20} Another

potential explanation for the lack of benefit seen in our study is the possibility that maximum bronchodilator effect had been achieved through albuterol administration early and now the primary disease burden was mediated through bronchial inflammation; this is supported by numerous studies demonstrating efficacy of magnesium administration early in hospital presentation^{5-7,21} with less benefit seen later in the disease course.¹⁰ Other potential reasons include the possibility that patients receiving magnesium may have been more ill than reflected by RAS, there were unaccounted for confounding factors, or that magnesium sulfate may not have a positive impact in the treatment of status asthmaticus outside the ED or intensive care setting. Deviation from hospital protocol in weaning albuterol for a RAS less than or equal to four or discharging after two doses of every 4 h albuterol treatments may also account for the lack of efficacy seen.

Additional limitations to our study include the small cohort of patients evaluated, potential bias in patient selection, lack of standardized criteria for magnesium administration, and its retrospective nature. Common side effects of magnesium infusion are usually mild, including transient facial warmth, flushing, dry mouth, and malaise.¹⁹ Significant adverse effects at therapeutic doses have not been reported but transient hypotension may be seen with rapid infusion.²⁰ No adverse events were attributed to magnesium therapy in our cohort, further demonstrating safety at commonly used doses.

5 | CONCLUSION

Children who require continuous albuterol therapy while inpatient can safely be administered intermittent magnesium sulfate outside the intensive care setting with low rates of significant adverse events; however, our study demonstrates no benefit of this therapeutic strategy. When compared to a cohort of similar illness severity, those who received magnesium did not experience shorter time on continuous albuterol or have shorter length of stay than those who did not receive magnesium. Given the high safety profile and strong evidence for magnesium sulfate administration in the emergency department, a well-designed randomized, double-blind control trial could help to further delineate the utility magnesium therapy for children on continuous albuterol therapy in the non-intensive care setting.

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CONFLICT OF INTEREST

The authors have no conflict of interest relevant to this article to disclose. No form of payment was given to anyone to produce the manuscript.

AUTHORS' CONTRIBUTION

RD and NA conceptualized and designed the study, carried out data collection, drafted the manuscript, and approved the final manuscript.

Both authors had full access to all the data during the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KH coordinated and organized data collection, carried out the initial analyses, completed final analyses, and approved the final manuscript. MH helped conceptualize the study, revised the manuscript, coordinated and supervised data collection, and approved the final manuscript.

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REFERENCES

1. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK7232/>.
2. Kenyon CC, Fieldston ES, Luan X, Keren R, Zorc JJ. Safety and effectiveness of continuous aerosolized albuterol in the non-intensive care setting. *Pediatrics*. 2014;134:e976–e982.
3. Craig VL, Bigos D, Brilli RJ. Efficacy and safety of continuous albuterol nebulization in children with severe status asthmaticus. *Pediatr Emerg Care*. 1996;12:1–5.
4. Bogie AL, Towne D, Luckett PM, Abramo TJ, Wiebe RA. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. *Pediatr Emerg Care*. 2007;23:355–361.
5. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child*. 2005;90:74–77.
6. Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA, Jr. Intravenous magnesium sulfate treatment for acute asthma in the emergency department: a systematic review of the literature. *Arch Dis Child*. 2005;90:74–77.
7. Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Cochrane Database Syst Rev*. 2016;4:CD011050.
8. Jaimovich DG. American academy of pediatrics committee on hospital care and section on critical care. Admission and discharge guidelines for the pediatric patient requiring intermediate care. *Pediatrics*. 2004;113:1430–1433.
9. Wisecup S, Eades S, Hashmi SS, Samuels C, et al. Diastolic hypotension in pediatric patients with asthma receiving continuous albuterol. *J Asthma*. 2015;52:693–699.
10. Shein SL, Farhan O, Morris N, Mahmood N, et al. Adjunctive pharmacotherapies in children with asthma exacerbations requiring continuous albuterol therapy: findings from the Ohio Pediatric Asthma Repository. *Hosp Pediatr*. 2018;8:89–95.
11. Ramprasad V, Amato I. Respiratory Assessment Score. Unpublished data, 2011.
12. Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10: pediatric advanced life support. The American heart association in collaboration with the International liaison committee on resuscitation. *Circulation*. 2000;102: I291–I342.
13. Scarfone RJ, Loiselle JM, Joffe MD, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med*. 2000;36:572–578.
14. Singhi S, Grover S, Bansal A, Chopra K. Randomised comparison of intravenous magnesium sulphate, terbutaline and aminophylline for children with acute severe asthma. *Acta Paediatr*. 2014;103: 1301–1306.
15. Ducharme FM, Chalut D, Plotnick L, et al. The pediatric respiratory assessment measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr*. 2008;152:476–480. 480.e1.
16. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med*. 2004;11:10–18.
17. Arnold DH, Saville BR, Wang W, Hartert TV. Performance of the acute asthma intensity research score for acute asthma research protocols. *Ann Allergy Asthma Immunol*. 2012;109:78–79.
18. Kokotajlo S, Degnan L, Meyers R, Siu A, Robinson C. Use of intravenous magnesium sulfate for the treatment of an acute asthma exacerbation in pediatric patients. *J Pediatr Pharmacol Ther*. 2014; 19:91–97.
19. Devi PR, Kumar L, Singhi SC, Prasad R, Singh M. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatr*. 1997;34:389–397.
20. Davalos Bichara M, Goldman RD. Magnesium for treatment of asthma in children. *Can Fam Physician*. 2009;55:887–889.
21. Rehder KJ. Adjunct therapies for refractory status asthmaticus in children. *Respir Care*. 2017;62:849–865.

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