Supplemental Online Content

Schuh S, Sweeney J, Rumantir M, et al. Effect of nebulized magnesium vs placebo added to albuterol on hospitalization among children with refractory acute asthma treated in the emergency department: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.19839

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix

1: Study

Sites

The lead investigators at each site are shown in **bold**.

eTable 1. Study Site Details

Site & Location	Average Emergency Department Annual Number of Visits	Number of Participants enrolled
The Hospital for Sick Children Toronto, Ontario, Canada	70,000	418
Alberta Children's Hospital Calgary, Alberta, Canada	75,000	130
Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada	52,000	16
Stollery Children's Hospital Edmonton, Alberta, Canada	50,000	38
Sainte-Justine Pédiatrie Montreal, Quebec, Canada	85,000	83
Children's Hospital of Eastern Ontario (CHEO) Ottawa, Ontario, Canada	75,000	78
British Columbia (BC) Children's Hospital, Vancouver, British Columbia, Canada	50,000	53

eAppendix 2:

Pediatric Respiratory Assessment Measure (PRAM)

PRAM is a 12-point pediatric asthma severity score validated in children between 1 and 17 years of age managed in the Emergency Department (ED) setting for acute asthma.
This instrument exhibits the most comprehensive measurement properties of all acute asthma scores and has been successfully used as an outcome in major trials.[1-3] *It is the only score with demonstrated criterion validity, using respiratory resistance as the gold standard.*[4] This instrument has been validated in both preschool and school aged children assessed in the ED for asthma exacerbations *and has strong association with admission, thus supporting its ability to distinguish across severity levels.*[5] *The score has inter-rater reliability consistently above 70%*[5] and is currently implemented in virtually all pediatric EDs across Canada.

Rationale for Selection of PRAM cut-off for Study Entry

Dr Ducharme had conducted an asthma audit at Montreal Children's Hospital and found that children with PRAM ≥5 points following initial bronchodilator therapy have at least a 30% probability of hospitalization and represent 84% of all acute asthma hospitalizations (personal communication-see below). Although the admission rate for children with PRAM ≥6 is higher, randomizing only this population would miss 30% of asthma hospitalizations. For these reasons, we have chosen PRAM ≥ 5 after initial front-line therapy as a marker of treatment-resistant asthma at a substantial risk of admission.

Mathematical Rationale for Oxygen Saturation in Calgary[6]

NASA equations for atmospheric pressure "p"

$$P = Po \times e^{-((g \times h \times M)/(To \times Ro))}$$

where Po is pressure at sea level in kilopascals (1013), g is the acceleration of gravity (9.8 m/sec^2), h is the height above sea level (Calgary is 1045 m above sea level), M is the molar mass of the earth atmosphere (0.029 kg/mol), To is standard temperature at sea level (288.16 deg K) and Ro is the universal gas constant ((8.31 J/(mol x K)). All of this works out to P = Po x 0.88.

When Po is expressed in mmHg, P_{bar} is 669 mmHg in Calgary. The alveolar gas equation is

$$P_{alv} = P_{bar} \times 0.21 - P_{CO2}/R$$

where 0.21 is the concentration of oxygen in air, P_{CO2} is the partial pressure of carbon dioxide and R is ratio of carbon dioxide production divided by oxygen consumption which is nominally 0.8 in the resting condition.

Hence P_{alv} at sea level is 760 x 0.21 – P_{CO2}/0.8. For a P_{CO2} of 40, P_{alv} is 110. For an A-a gradient of 10 assumed in normoxemic people, P_{art} is 100 mmHg. However, for Calgary with a P_{bar} of 669, the P_{alv} is 90 and the P_{art} is 80. From the oxygen dissociation curve, this would represent about a 2% difference in oxygen saturation which is what we used in the Calgary PRAM score.

If you have questions/comments about the various models, contact:

Dr. Dieter K. Bilitza, bilitza@mail630.gsfc.nasa.gov, Mail Code 612.4, NASA/Goddard Space Flight Center, Greenbelt, MD 20771

NASA Official: Dr. Robert McGuire, Head of the Space Physics Data Facility

eTable 2. Pediatric Respiratory Assessment Measure Scores in Triage and After Initial Bronchodilator Therapy [a]

Triage PRAM	N	Post-Bronchodilator Therapy PRAM ≥ 5
4	74	16 (22%)
5	69	24 (35%)
6	88	45 (51%)
7	50	34 (68%)
8	32	25 (78%)
9	18	15 (83%)
10	10	8 (80%)
11	11	11 (100%)

Of children with PRAM ≥5 in triage, 58% (162/278) have post-bronchodilator therapy PRAM of ≥ 5.

[a]2006 Asthma audit from Montreal Children's Hospital

eTable 3. Post-Bronchodilator PRAM Score as a Proportion of Asthma Hospitalizations

Post-Bronchodilator PRAM score	Proportion of asthma hospitalizations
PRAM ≥ 4	97%
PRAM ≥ 5	84%
PRAM ≥ 6	71%
PRAM ≥ 7	49%

[a]2006 Asthma audit from Montreal Children's Hospital

eAppendix 3:

Procedures Related to Blinding and Kit Preparation

These procedures were itemized in the manual of operations prepared by Darcy Nicksy, a collaborating Research Pharmacist at the principal center. The identical iso-osmolarities of the Mg and placebo solutions were determined by DN prior to the start of the study.

eTable 4. Logistics of Blinding and Kit Making

Study Arm	Investigational Drug or Placebo (mg=mL) (Blinded Vial in Kit)	Salbutamol Nebulizer Solution 5mg/mL Open Label Bottle (mg=mL)	Sterile Water for Injection Diluent: Volume to Top up to 6mL Final Volume [Open Label Bottle] (mL)	Osmolarity of the final mixed solution to be nebulized (mOsm/L)
Active Arm	Magnesium Sulfate Injection 500mg/mL, 7 mL repackaged multidose vial (600mg Mg Sulf = 1.2mL)	Dose:5mg = 1mL	Sterile Water for Injection (3.8mL)	**384**
Placebo Arm	Hypertonic Saline (5.5%), 7 mL compounded multidose vial (Dose: 0mg Mg Sulf = 1.2mL)	Dose: 5mg = 1mL	Sterile Water for Injection (3.8mL)	**381**

Each site prepared consecutively numbered randomization kits, numbered according to the site's Master Randomization table. Each kit will contain:

- **Magnesium Sulfate** Injection 500mg/mL OR **Hypertonic Saline** (5.5%)
    - **Active kits** contain Magnesium Sulfate injection
        - Injection to be administered by nebulized inhalation
        - Unblinded site pharmacy repackaged small batches of Canadian commercial Magnesium injection into empty sterile vials in a laminar air flow hood according to detailed worksheet procedures in the Pharmacy Manual of Operations.
    - **Placebo Kits** contain Hypertonic Saline 5.5%
        - Unblinded site pharmacy compounded small batches of Hypertonic Saline (5.5%) in a Laminar Air Flow hood using 14.6% concentrated Sodium Chloride and sterile water according to detailed worksheet procedures in the Pharmacy Manual of Operations.
        - ***Hypertonic Saline (5.5%) was chosen as the Placebo since Magnesium Sulfate is hypertonic. 5.5% is the percentage that mimicks the osmolality of the Active arm when sterile water is used as the top up diluent.***
    - The repackaged Magnesium Sulfate and compounded placebo vials were given a 6 month expiry date.
    - During Kit assembly by the site pharmacy, identical labels were placed on the blinded vials in order to ensure the integrity of the blind.
    - Blinded Numbered Randomization Kits were assembled by the unblinded site pharmacy and made available to the Emerg Study RNs for use once a subject is eligible to be randomized

Open Label supplies of the following were available:

- Salbutamol Nebulizer Solution 5mg/mL
    - Canadian commercial supply. No blinding required.
    - Drug accountability according to Health Canada Division 5 regulations will be maintained

- Sterile Water for Injection (SWI)
  - Used as the diluent to top up to final 6mL nebulizer volume
  - Canadian commercial supply. No blinding required.
  - Drug accountability according to Health Canada Division 5 regulations were maintained
  - ***Sterile Water was chosen as the top up diluent to ensure that the final osmolality of the nebulizer solutions was less than 500 (the osmolality at which bronchospasm has been reported). The inhalation solutions in both study arms was of comparable isotonicity.***

In this Investigator- initiated study, the numbered kits were assembled and labeled in the local Research Pharmacy according to detailed kit making Standard Operating Procedures provided by the Coordinating Pharmacy at SickKids. All kits/products had appropriate Clinical Trial labeling according to Canadian regulations.

eAppendix 4:

Emergency Unblinding Procedures[a]

In the unlikely event the patient develops hypotension requiring therapy, apnea, heart block or another adverse event and the ED physician feels that the experimental therapy cannot be safely continued, further doses of the experimental treatment were to be stopped. If these adverse events are accompanied by severe distress and additional IV Mg is warranted, the study may be unblinded for that subject. If the subject was allocated to the Active Mg Sulfate arm, then additional IV Mg should not be given but alternative treatment provided instead. If the subject was allocated to the Placebo arm, then IV Mg may be given as part of treatment of the adverse event. Emergency unblinding should only be requested when the clinical treatment of the patient would be different by knowing which arm of the study the patient was previously on. The study PI/local PI and the study nurses to remain blinded if possible.

The following Emergency Unblinding procedure were to be followed:

1. Treating Physician or RN should contact the local PI of the study for consultation to unblind. In the event they cannot be reached immediately go to the next step.

2. Contact the SickKids hospital pharmacy by phone.

3. Provide the patient's study randomization number, reason for unblinding, your site and your name to the SickKids pharmacist who will then provide the unblinded study arm.

4. Note that all patients whose therapy is unblinded must stop taking the experimental therapy The ED physician will prescribe additional treatment as clinically appropriate.

5. The requesting physician should initiate Email communication within 24 hours detailing the request for Emergency unblinding and why. The email must inform the local PI and SickKids Research Pharmacist and Study PI.

6. The local DSMC and REB will be advised of emergency unblinding within 48 hours.

[a]There were no instances of treatment allocation unblinding during this trial.

eAppendix 5:

The Selection of the Delivery System for Inhaled Magnesium in the Trial

One of the challenges inherent to the delivery of $MgSO_4$ is the relative lack of efficacy of this drug, compared to other bronchodilators used to treat acute asthma. While most inhaled asthma medications (such as albuterol) are active in the microgram range, $MgSO_4$ is only active in the milligram range. One reason for negative results in some of the previous studies of inhaled $MgSO_4$ may have been that the nebulizer systems employed were relatively inefficient and did not deliver sufficient amount of $MgSO_4$ to achieve efficacy. The other constraint was the need to use the same delivery system over a wide patient age range of 2 to 17 years.

As part of our pilot work, we compared a number of aerosol delivery systems and breathing patterns and chose to use a vibrating mesh nebulizer, the AeroNebGo, coupled with the valve-less holding chamber, the Idehaler in order to optimize efficiency of $MgSO_4$ delivery.[7] Previously published *in vitro* studies demonstrated that both the breathing pattern and the respirable fraction were age-dependent[8], and suggested there would be a very similar Mg deposition in terms of mg/kg body weight over a wide range of body sizes in our trial population. These *in vitro* data were indeed supported by our subsequent *in vivo* nuclear medicine deposition pilot work.[9]

eAppendix 6:

Study Conduct

Data Monitoring Committee met yearly to provide study oversight.

The Data Monitoring Committee consisted of Dr Patricia Parkin (Division of Pediatric Medicine, the Hospital for Sick Children)-chair, Dr Neil Sweezey (Division of Respiratory Medicine, the Hospital for Sick Children), Annie Dupuis (Statistician, Research Institute, the Hospital for Sick Children), and Judy Sweeney, the MAGNUM PA study manager.

The principle investigative site conducted periodic quality assurance audits at all sites. The collaborating Research Pharmacist (D.N.) at the principle investigative site prepared the randomization tables for all participating sites and a detailed manual of operations distributed to all site pharmacies. Study kits were prepared by the collaborating site pharmacies. Study data management was contracted out to Cardiovascular Data Management Centre & Computational Biomedicine Program at the Hospital for Sick Children.

All authors assume responsibility for the accuracy of the manuscript and vouch for its completeness and fidelity to the study protocol.

eAppendix 7:

Changes in Secondary Outcomes Over Time

(Please see p. 10 for eTable 5 – “Changes in secondary outcomes over time”)

eTable 5. Changes in Secondary Outcomes Over Time[a]

Outcomes mean(SD)	Mg group pre-intervention	Mg group post-intervention	Adjusted Difference[b] 95% CI	Placebo group pre-intervention	Placebo group post-intervention	Adjusted Difference[b] 95% CI	Adjusted Difference in-differences[b], 95% CI	p-value
PRAM[c]								
60 minutes	6.18 (1.33)	4.01 (1.86)	2.18 (2.01–2.35)	6.37 (1.27)	4.46 (1.68)	1.91 (1.74-2.08)	0.27 (0.03-0.51)	0.03
120 minutes	6.18 (1.33)	3.90 (1.87)	2.31 (2.13-2.49)	6.37 (1.27)	4.13 (1.88)	2.24 (2.06-2.42)	0.07 (-0.19-0.32)	0.60
180 minutes	6.18 (1.33)	3.73 (1.82)	2.51 (2.30-2.71)	6.37 (1.27)	3.97 (1.79)	2.43 (2.23-2.63)	0.08 (-0.21-0.36)	0.59
240 minutes	6.18 (1.33)	3.84 (1.94)	2.43 (2.16 - 2.69)	6.37 (1.27)	4.13 (2.04)	2.29 (2.03 - 2.54)	0.14 (-0.23 – 0.51)	0.45
Respiratory rate								
60 minutes	38.09 (9.41)	35.16 (8.94)	3 (2.29-3.71)	38.21 (9.86)	37.14 (10.07)	1.07 (0.37-1.77)	1.93 (0.93-2.92)	0.0002
120 minutes	38.09 (9.41)	34.66 (8.52)	3.46 (2.69-4.24)	38.21 (9.86)	35.62 (9.05)	2.58 (1.82-3.34)	0.88 (-0.20-1.97)	0.11
180 minutes	38.09 (9.41)	33.94 (8.61)	4.5 (3.59-5.41)	38.21 (9.86)	34.51 (8.82)	3.75 (2.86-4.64)	0.75 (-0.52-2.02)	0.25
240 minutes	38.09 (9.41)	34.35 (8.86)	4.12 (3.04 - 5.19)	38.21 (9.86)	34.54 (8.86)	3.81 (2.78 - 4.83)	0.31 (-1.17 - 1.79)	0.68
Oxygen saturation								
60 minutes	94(3.11)	95.30 (2.86)	-1.32 (-1.58- -1.07)	94.20 (3.07)	95.23 (2.92)	-1.03 (-1.28- -0.77)	-0.30 (-0.66-0.06)	0.10
120 minutes	94(3.11)	95.02 (2.94)	-1.12 (-1.37- -0.86)	94.20 (3.07)	95.21 (2.74)	-0.98 (-1.24- -0.73)	-0.13 (-0.50-0.23)	0.48
180 minutes	94(3.11)	94.84 (2.90)	-1.08 (-1.37- -0.78)	94.20 (3.07)	95.28 (2.85)	-1.12 (-1.41- -0.83)	0.04 (-0.37-0.46)	0.83
240 minutes	94(3.11)	94.50 (3.04)	-0.91 (-1.27 - -0.55)	94.20 (3.07)	94.86 (2.96)	-0.87 (-1.21 - -0.52)	-0.05 (-0.54 – 0.45)	0.86
Systolic blood pressure								
20 minutes	108.44 (11.82)	110.29 (11.71)	-1.61 (-2.63- -0.59)	108.04 (10.75)	108.83 (11.26)	-0.80 (-1.81-0.21)	-0.81 (-2.25-0.62)	0.27
40 minutes	108.44 (11.82)	110.90 (11.90)	-2.19 (-3.31- -1.07)	108.04 (10.75)	108.42 (11.30)	-0.29 (-1.37-0.79)	-1.90 (-3.45- -0.34)	0.02
60 minutes	108.44 (11.82)	110.44 (10.42)	-1.77 (-2.86- -0.69)	108.04 (10.75)	108.00 (11.21)	0.10 (-0.97-1.17)	-1.87 (-3.40- -0.35)	0.02
120 minutes	108.44 (11.82)	108.34 (10.61)	0.2 (-0.96-1.35)	108.04 (10.75)	107.70 (10.97)	0.41 (-0.74-1.55)	-0.21 (-1.83-1.42)	0.80
180 minutes	108.44 (11.82)	107.92 (10.03)	0.49 (-0.75-1.74)	108.04 (10.75)	107.93 (11.97)	0.31 (-0.89-1.51)	0.18 (-1.55-1.91)	0.84
240 minutes	108.44 (11.82)	108.31 (12.41)	0.09 (-1.55 – 1.7)	108.04 (10.75)	108.77 (12.96)	-0.52 (-2.05 –1.0)	0.61 (-1.64 - 2.85)	0.60
Diastolic blood pressure								
20 minutes	62.59 (11.24)	64.47 (10.50)	-1.74 (-2.90- -0.58)	63.13 (10.65)	61.09 (11.55)	2.03 (0.88-3.17)	-3.76 (-5.39- -2.13)	<.0001
40 minutes	62.59 (11.24)	63.50 (10.51)	-0.68 (-1.96-0.6)	63.13 (10.65)	60.79 (11.63)	2.38 (1.13-3.62)	-3.06 (-4.84- -1.27)	0.0008
60 minutes	62.59 (11.24)	62.19 (9.97)	0.55 (-0.62-1.72)	63.13 (10.65)	59.25 (11.64)	3.94 (2.78-5.09)	-3.38 (-5.03 - -1.74)	<.0001
120 minutes	62.59 (11.24)	60.39 (10.18)	2.3 (1.05-3.56)	63.13 (10.65)	59.80 (11.35)	3.38 (2.13-4.62)	-1.07 (-2.84-0.70)	0.23
180 minutes	62.59 (11.24)	60.55 (10.45)	2.2 (0.78-3.62)	63.13 (10.65)	58.75 (11.26)	4.51 (3.14-5.88)	-2.31 (-4.29- -0.34)	0.02
240 minutes	62.59 (11.24)	59.64 (11.62)	3.04 (1.34 - 4.74)	63.13 (10.65)	58.85 (10.47)	4.39 (2.78 - 6.00)	-1.35 (-3.70 - 0.99)	0.26

[a] All comparisons have controlled for stratification at randomization for site and age group.
[b] Difference from randomization baseline to the specific time point.
[c] PRAM represents Pediatric Respiratory Assessment Measure. See Table 1 for score calculation and severity interpretation.

eAppendix 8:

Pediatric Emergency Research Canada (PERC) Authors

Pediatric Emergency Research Canada (PERC) authors on this study are:

Suzanne Schuh, MD, FRCPC
Judy Sweeney, RN, BScN
Maggie Rumantir, MD
Yaron Finkelstein, MD, FACMT
Graham Thompson, MD, FRCPC
Roger Zemek, MD, FRCPC
Amy C. Plint, MD, MSc
Jocelyn Gravel, MD, MSc, FRCPC
Francine M Ducharme, MD, MSc, FRCPC
David W. Johnson, MD
Karen Black, MD, MSc, FRCPC
Sarah Curtis, MD, FRCPC
Darcy Beer, MD, FRCPC
Terry P Klassen, MD, MSc, FRCPC
Stephen B. Freedman, MDCM, MSc

eReferences

1. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. *The Journal of pediatrics*. 2000;137(6):762-768.
2. Birken CS, Parkin PC, Macarthur C. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity, and responsiveness. *Journal of clinical epidemiology*. 2004;57(11):1177-1181.
3. Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *The New England journal of medicine*. 2009;360(4):329-338.
4. Ducharme FM, Davis GM. Respiratory resistance in the emergency department: a reproducible and responsive measure of asthma severity. *Chest*. 1998;113(6):1566-1572.
5. Ducharme FM, Chalut D, Plotnick L, Savdie C, Kudirka D, Zhang X, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *The Journal of pediatrics*. 2008;152(4):476-480, 480 e471.
6. (COESA) USCoEttSA. U.S. Standard Atmosphere 1976. U.S. Government Printing Office, Washington, D.C.1976 1976. Report No.: Product Number: ADA-035-6000.
7. Coates AL, Leung K, Vecellio L, Schuh S. Testing of Nebulizers for Delivering Magnesium Sulfate to Pediatric Asthma Patients in the Emergency Department. *Respir Care*. 2011;56(3):314-318.
8. Coates AL, Tipples G, Leung K, Gray M, Louca E, Vaccine WPDGfMA. How many infective viral particles are necessary for successful mass measles immunization by aerosol? *Vaccine*. 2006;24(10):1578-1585.
9. Coates AL, Leung K, Chan J, Ribeiro N, Charron M, Schuh S. Respiratory system deposition with a novel aerosol delivery system in spontaneously breathing healthy adults. *Respir Care*. 2013;58(12):2087-2092.