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Asthma Frequently Asked Questions

Question 5: Magnesium Sulphate for Acute Asthma in children

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Educational aims

After reading this article the reader will:

- Understand the mechanisms of action and rationale for MgSO4 use in acute asthma.
- Summarise the evidence base for the use of MgSO4 in acute asthma.
- Compare and contrast the recent literature focusing on the use of intravenous and nebulised MgSO4.
- Apply this knowledge to their clinical management of acute asthma.
- Employ this understanding to their critical appraisal of acute asthma studies.

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ABSTRACT

Most children who present to the emergency department with acute asthma, respond well to inhaled β_2-agonists (spacer or nebuliser), oxygen (if required) and systemic steroids. Guidelines across the world agree on this simple, straight forward evidenced based approach. In children with more severe asthma attacks and those who do not respond to initial treatment, the evidence base for the secondary level treatment is less clear. Many regimens exist for the next step. Intravenous Magnesium Sulphate ($MgSO_4$) is now used frequently in these situations and some centres are starting to use nebulized $MgSO_4$ as part of the initial maximal inhaled therapy options. This paper examines the role of $MgSO_4$ in acute asthma in children. It focusses on how $MgSO_4$ might work, what are the current recommendations for use and then what is the current evidence base to support its use. We have presented the evidence for the use of both nebulized and intravenous $MgSO_4$. At the end of the paper we have suggested future directions for research in this area. Our aim is to present a synthesis of the current role of $MgSO_4$ in the management of an acute asthma attack.

INTRODUCTION

An acute attack of asthma and acute wheezing is one of the leading causes of visits to the Paediatric Emergency Department (PED) and hospitalisation in children [1]. An asthma attack is defined as an *"acute or sub-acute episode of progressively worsening shortness of breath, cough, wheezing, and chest tightness or some combination of these symptoms"* [1]. First-line therapy for management of an acute exacerbation of asthma is well established and consists of oxygen delivery (when hypoxic) and inhalation either by spacer or nebuliser of intermittent inhaled short-acting $beta_2$-agonists (SABAs) and oral corticosteroids [1–4]. In severe episodes, there is evidence to suggest that additional inhaled ipratropium bromide is of benefit [5].

When the exacerbation is severe, or unresponsive to initial treatment, other treatment options include intravenous (IV) bronchodilators (such as salbutamol, magnesium sulphate ($MgSO_4$), terbutaline or aminophylline), nebulised $MgSO_4$, inhaled *Heliox*, intravenous ketamine and non-invasive or invasive respiratory support [1–4].

There is no established consensus about the precise order in which these additional therapies should be used. This is partially due to the lack of robust evidence. Some studies lack statistical

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power and meta-analysis is complicated by the different definitions of an acute severe attack used and the variability of primary outcomes reported in studies [6].

National, international and hospital best practise guidelines from around the world all vary in their recommendations [1–4]. There is obvious variation in practise in different hospital and geographical areas. A recent survey of emergency physicians in the United Kingdom and Ireland found that over half of frontline Emergency Physicians and General Paediatricians preferred salbutamol as first line intravenous treatment, while 28% preferred $MgSO_4$, and 15% preferred aminophylline [7]. An earlier survey of paediatric emergency specialists in Australia and New Zealand found that aminophylline was used by 45%, intravenous $MgSO_4$ by 55%, and intravenous salbutamol by 87% of respondents as sole therapy but also in combination of two or all three [8]. A prospective study in 24 EDs in the United Kingdom and Ireland found wide variation in the prevalence of intravenous treatment for acute paediatric asthma ranging from 0% to 19.4% [9]. Of the 178 clinicians who replied to the question, 99 (55.6%) used salbutamol as first-line intravenous therapy, 52 (29.2%) $MgSO_4$ and 27 (15.2%) aminophylline; 87 (48.9%) give these sequentially depending on response and 30 (16.8%) give them concurrently. So $MgSO_4$ is being used regularly in severe acute asthma in children by the intravenous route throughout the world.

There are currently no data describing the current use of nebulised $MgSO_4$ in the UK or Australia. In a recent review of the role of $MgSO_4$ in adult acute asthma, it was concluded that there was no strong evidence on the beneficial effects of either IV or nebulised $MgSO_4$ in the treatment of severe acute asthma [in adults], when optimal treatment options are available [10]. They also highlighted that it appears that the clinical significance of $MgSO_4$ in everyday practise is overestimated. There is certainly good evidence that it is used widely in children during acute attacks. This aim of this paper is to explore the recent evidence on the use of $MgSO_4$ in both modalities for acute severe asthma in children.

WHY USE MAGNESIUM IN ACUTE ASTHMA AND WHEEZING?

Magnesium is one of the most common cations in the human body. It is found mainly in bones and intracellularly in the body organs and blood serum contains only 1% of the total. The absorption of magnesium is mainly in the small intestine. It is eliminated from the body by the kidney and in sweat [11]. Magnesium plays a role in the cellular homeostasis and enzymatic reactions in the body [11].

The role of magnesium in asthma is not clearly understood though there are many studies dating back to 1912, which have attempted to explain its mechanism of action in vivo. Magnesium has significant bronchodilator effects and it causes relaxation of bronchial cells in vitro [12]. Magnesium activates the sodium-calcium pumps in the endoplasmic reticulum and thereby decreases the release of intracellular calcium in smooth muscles by blocking its entry and its release from the endoplasmic reticulum. This inhibition of calcium's interaction with myosin results in muscle cell relaxation.

Magnesium also stabilisesT cells and prevents the mast cell degranulation which in turn causes the inflammatory mediators to reduce. Magnesium may also be beneficial in an acute attack as it stimulates the release of nitric oxide and increases prostacyclin synthesis [12]. Finally, magnesium ions may have an anti-inflammatory role, attenuating neutrophil activation in adults with asthma [13]. In a guinea pig model of asthma and $MgSO_4$ use, there is good evidence of a dose response and the bronchodilator effect and a synergism with salbutamol. Salbutamol and magnesium result in a greater bronchodilator and anti-inflammatory response when used together, when compared to individual responses of either used alone [14]. These responses need further exploration in human studies.

WHAT ARE THE RECOMMENDATIONS FOR THE USE OF $MGSO_4$ IN ACUTE ASTHMA MANAGEMENT IN CHILDREN?

In 2020 GINA guidelines states that IV $MgSO_4$ is not recommended in children, although there is evidence that it could work in children who do not respond to initial standard therapy. GINA does not recommend the routine use of nebulized $MgSO_4$ in acute asthma, although there was reported improvement in lung function parameters in children with severe exacerbations [2]. The 2014 British Thoracic Society (BTS) Guidelines did not recommend using nebulized $MgSO_4$ in children with asthma attacks and they stated that this required the need for more supporting evidence. However the updated BTS guideline in September 2016 recommended considering the use of nebulised $MgSO_4$ at 150 mg per dose in acute asthma management [3]. The 2016 BTS revised guideline recommended 40 mg/kg IV $MgSO_4$ for those not responding to initial treatment of standard bronchodilators. The recommendation from the American Thoracic Society Guidelines 2016 is that intravenous magnesium sulphate has no value in patients with mild exacerbations but to be considered in those who present with life threatening exacerbations and if the exacerbations remain severe even after one hour of intensive conventional treatment [1]. The NAC Australia [4] recommends IV $MgSO_4$ as second-line and third-line bronchodilators for children in Australian guidelines. There is no mention of nebulised $MgSO_4$.

WHAT IS THE CURRENT EVIDENCE FOR THE USE OF $MGSO_4$ IN ACUTE ASTHMA MANAGEMENT IN CHILDREN?

We conducted a systematic literature review using PubMed, Embase, CINAHL, Cochrane Database and the Web of Science using the search terms Asthma, Magnesium sulphate and children. We only included publications from the last 10 years. Appropriate keywords and synonyms were used for maximum recall and precision. This strategy identified a total of 379 citations after removing the duplicates using EndNote citation management software. This search was re-run again in December 2019 and there were no further papers to add to the review. We identified 5 systematic reviews, 6 recent studies examining nebulised $MgSO_4$ and 6 recent studies examining intravenous $MgSO_4$.

NEBULISED $MGSO_4$ IN ACUTE ASTHMA

The conclusion from the most recent Cochrane review in 2018 on acute asthma [15] treatment in children with nebulised $MgSO_4$ was that it may result in modest additional benefits for lung function and hospital admission when added to inhaled β_2-agonists and ipratropium bromide, but the reviewers' confidence in the evidence was low and there remains substantial uncertainty. Nebulised $MgSO_4$ does not appear to be associated with an increase in serious adverse events. There were 24 trials in this review update but unfortunately the authors were unable to pool data for all outcomes of interest and this has limited the strength of the conclusions reached. This is particularly important in paediatric studies where measuring lung function at the time of an exacerbation may not be possible. One large study [MAGNETIC] suggested that those with more severe attacks and attacks of shorter duration may experience a greater benefit but this was only in statistically significant changes in asthma severity score which may not reflect clinically important differences [16].

The aim of the MAGNETIC study was to assess whether there was any clinical benefit to adding nebulised $MgSO_4$ (150 mg per nebulised treatment every 20 min) to standard inhaled therapy comparing to standard treatment alone. This was a multicentre randomised placebo controlled trial in UK, involving the emergency departments (ED) of 30 hospitals with 503 subjects presenting with acute severe asthma in children between the ages of 2–15 yrs. The primary outcome measure was the change in asthma severity score. Secondary outcomes included the stepping down of treatment, reduction of stay in hospital, avoiding the need for IV drugs and avoiding PICU admission.

The authors' concluded that the study supported the use of nebulised isotonic $MgSO_4$ in the first hour of treatment as an add-on to standard bronchodilator treatment when a child presents with an acute episode of severe asthma. The study noted in a planned subgroup analysis, that in children who presented with more severe attacks (defined by more marked asthma severity score) and shorter duration of exacerbations the effect of treatment with nebulized magnesium was more marked [16].

Subsequent studies have failed to demonstrate a statistically significant beneficial effect. Alansari K et al. recruited 365 children to a placebo controlled study of nebulized $MgSO_4$ recruited from a single Paediatric Emergency Centre in Doha Qatar. A total of 191 children received active treatment, and 174 children received nebulised placebo alongside standard therapy [17]. The groups were similar with mean baseline asthma severity scores. This team used a total of 800 mg (266 mg every 20 min for an hour) a higher dose than the MAGNETIC study [16].

Accelerated failure time analysis showed a non-significantly shortened time to medical readiness for discharge of 14% favouring the $MgSO_4$ group (OR = 1.14: 95% CI 0.93–1.40, $p = 0.20$). Mean times until readiness for discharge were 14.7 h [SD 9.7] versus 15.6 h [SD 11.3] for the investigational and placebo groups, respectively, $p = 0.41$. Serum magnesium assays were taken before and after treatment and not associated with toxic levels. These authors concluded that adding nebulised magnesium to combined nebulized bronchodilator and systemic steroid therapy failed to significantly shorten time to discharge of children with moderate or severe asthma.

The MagNUM-PA study is currently recruiting in children [18]. It is interesting that these authors have highlighted that the dose of $MgSO_4$ has varied seven-fold among paediatric studies and only one study limited participants to non-responders to bronchodilators. The other limitations of past paediatric studies are: failure to limit participants to non-responders to bronchodilators, inadequate use of anticholinergics, use of inefficient delivery methods, small sample size, recruitment of children with less severe exacerbations and recruitment of children without an established diagnosis of asthma and were presenting for the first time with acute wheeze.

The MagNUM-PA study is focusing on children with an established diagnosis of asthma who are suffering a more severe exacerbation which has failed to respond to optimised baseline acute asthma therapy. They are using a much higher dose of $MgSO_4$ (600 mg per nebulised treatment every 20 min; total dose 1800 mg in an hour) and a nebuliser device which has been shown to deliver a higher proportion of nebulised drug into the lungs compared to standard nebulisers. The primary outcome is admission to hospital and the asthma severity score is one of the secondary outcomes. This study highlights the issue of there being lack of agreement on what outcomes should be measured in and acute asthma study in children. There have been recent calls for adoption of a worldwide standardised core outcome set for acute asthma studies [15,18].

The area remains controversial. A recent systemic review from 2018 suggested that there was no effect of nebulised $MgSO_4$ on respiratory function or hospitalisation [19] in acute asthma in children. The authors chose to include two studies which were not included in the Cochrane review [15], both published in 2014 [20,21]. These were limited by heterogeneity of patient inclusion (all severities from mild to severe) and relatively small numbers (80 subjects [20] in one study from Iran and 220 subjects from a study from China [21]. Their reported outcomes included asthma severity score (the Pulmonary Index), lung function (FEV_1 and PEFR).

One recent further underpowered study using the 150 mg dose of $MgSO_4$ every 20 min in mild to moderate acute asthma with 16 patients receiving $MgSO_4$ and 17 patients receiving nebulised ipratropium and fenoterol along with salbutamol showed no difference in PRAM score or length of hospital stay [22]. Again this illustrates differences in definitions, interventions and outcomes used which makes the literature weaker when it comes to comparisons and making firm conclusions.

INTRAVENOUS $MGSO_4$ IN ACUTE ASTHMA

Earlier systematic reviews from 2007 and 2013 [23,24] concluded that using intravenous (IV) $MgSO_4$ during acute asthma exacerbations in children may decrease hospital admission and improves lung function. The more recent Cochrane review [25] on IV $MgSO_4$ published in 2016 included studies published before February 2016 and the meta-analysis by Su et al. [18] considered studies dated until June 2015.

Considering IV $MgSO_4$ is used so frequently in children with asthma the evidence is relatively weak. It is based on six studies [26–31] made up of 325 children, the largest of these included just 143 participants [31]. The included studies were considered to have an overall low risk of bias, but any analysis is plagued by small sample sizes. Treatment with IV $MgSO_4$ reduced the odds of admission to hospital by 68% (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.14–0.74). Griffiths et al. also performed meta-analysis for the outcome 'return to the emergency department within 48 h', which showed a very imprecise effect estimate that was not statistically significant (OR 0.40, 95% CI 0.02–10.30). Side effects and adverse events were not consistently reported and meta-analysis of these was not possible, however few side effects or adverse events were reported.

Despite its limitations, the most recent Cochrane review reasonably concluded that IV $MgSO_4$ may reduce the need for hospital admission in children presenting to the ED with moderate to severe exacerbations of asthma, but noted that the evidence was limited by the number and size of studies [25]. Few side effects of the treatment were reported, but again the data were extremely limited.

The forest plots in the last meta-analysis showed that IV $MgSO_4$ had a positive impact on admission to hospital [risk ratio of 0.70 (95%CI; 0.54–0.90)] and need for mechanical ventilatory support [risk ratio 0.16 (95%CI; 0.06–0.44)]. This warrants further discussion.

The study of Torres [31] which was included in the analysis was an open non blinded study. Moreover, they reported an intubation rate of 30%. This very high rate of requirement for mechanical ventilation may have introduced bias to any analysis. These studies also have the issues of heterogeneity with differences in inclusion criteria, definitions of disease, interventions and primary and secondary outcomes. Doses of intravenous $MgSO_4$ varied in the studies from 25 to 100 mg/kg infusion over 25–30 min.

The conclusions from the most recent meta-analysis is that intravenous $MgSO_4$ IV should be given to those with the more severe exacerbations that have not responded to initial standard inhaled treatment [18].

DIRECTIONS FOR FUTURE RESEARCH

Use of nebulised $MgSO_4$ delivered using the most efficient methods [17,18] seems to have the benefits of easy delivery, low cost and limited side effects. There is still no definite evidence to suggest that there is major benefit clinically in terms of improvement in lung function, reduction of readmission to ED, need for intravenous bronchodilators and admission to the paediatric Intensive care unit (PICU). There is a suggestion that those with a more severe exacerbation and of shorter history there may be some benefit. However with the more detailed studies ongoing looking at higher doses, more severe exacerbations and better delivery systems there may be further evidence of a role. There should be further studies on dose–response and pharmacokinetics to identify what should be the ideal dose to use in the nebuliser. If progress is to be made in determining the best place for nebulised $MgSO_4$ in paediatric asthma then we need sufficiently powered placebo-controlled trials targeting children with asthma who are not responding to standard maximal treatment, including inhaled β_2-agonists and ipratropium bromide and systemic steroids. They require appropriate doses and delivery systems and the evidence to date suggests that those with more severe attacks with a shorter history should be the focus for future studies.

It is still remarkable that the evidence base for the use of intravenous $MgSO_4$ is made up of only 325 cases with only six small powered studies, some with high risk of bias. Certainly further data are required here and in a more severe acute group of children. There are data to suggest that $MgSO_4$ augments to response of the beta receptors to salbutamol [14] so perhaps studies should include the joint administration contemporaneously of these two medications. This practise is already occurring without the evidence base to support it [9]. There are also data now about the role of continuous infusions of IV $MgSO_4$ (200 mg/kg over 4 h) rather than a short bolus of IV $MgSO_4$ [32]. This needs further consideration. We do not have a study in children similar to the 3 Mg in adults [33] study where IV $MgSO_4$ is directly compared to nebulised $MgSO_4$ at the higher doses. Most importantly in order to make comparisons of studies, the paediatric acute asthma research community need to have a further standardisation of definitions, interventions and outcomes, so we can make compare studies more fruitfully. There should be a core data set established in all acute asthma studies with an international agreement on how acute asthma intervention studies should be carried out and what core outcomes should be collated [6].

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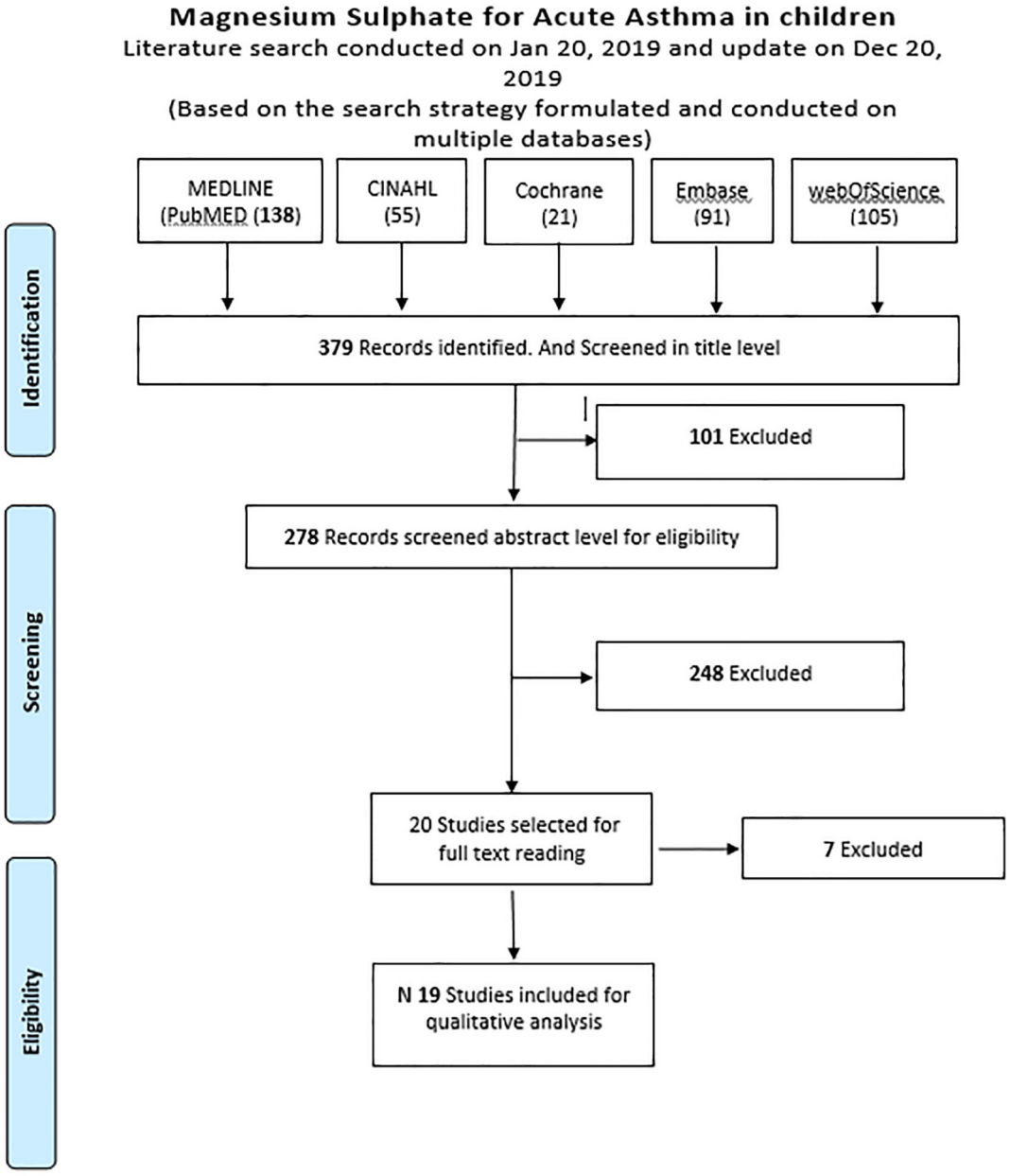
None.

APPENDIX 1



Adapted From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

References

[1] Program NAE, Expert P. Panel Report 3 (EPR- 3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120:S94–S138. https://doi.org/10.1016/j.jaci.2007.09.043.

[2] From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2020. Available from Global Initiative for Asthma (GINA) 2020. http://ginasthma.org/.

[3] Network SIG, Society BT. British guideline on the management of asthma: A national clinical guideline n.d. https://www.sign.ac.uk/assets/sign158.pdf.

[4] National Asthma Council Australia. The Australian Asthma Handbook 2019. https://www.asthmahandbook.org.au/.

[5] Powell CV, Cranswick NE. The current role of ipratropium bromide in an acute exacerbation of asthma. J Paediatr Child Health 2015;51:751–2. https://doi.org/10.1111/jpc.12890.

[6] Gray CS, Powell CVE, Babl FE, Dalziel SR, Craig S, Network P (Paediatric RIEDICR). Variability of outcome measures in trials of intravenous therapy in acute severe paediatric asthma: a systematic review. Emerg Med J 2019;36:225–30. https://doi.org/10.1136/emermed-2018-207929.

[7] Lyttle MD, O'Sullivan R, Doull I, Hartshorn S, Morris I, Powell CVE, et al. Variation in treatment of acute childhood wheeze in emergency departments of the United Kingdom and Ireland: an international survey of clinician practice. Arch Dis Child 2015;100:121–5. https://doi.org/10.1136/archdischild-2014-306591.

[8] Babl FE, Sheriff N, Borland M, Acworth J, Neutze J, Krieser D, et al. Paediatric acute asthma management in Australia and New Zealand: practice patterns in the context of clinical practice guidelines. Arch Dis Child 2008;93:307–12. https://doi.org/10.1136/adc.2007.125062.

[9] Morris I, Lyttle MD, O'Sullivan R, Sargant N, Doull IJM, Powell CVE, et al. Which intravenous bronchodilators are being administered to children presenting with acute severe wheeze in the UK and Ireland? Thorax 2015;70:88–91. https://doi.org/10.1136/thoraxjnl-2014-206041.

[10] Javor E, Grle SP. Limitations of the results from randomized clinical trials involving intravenous and nebulised magnesium sulphate in adults with severe acute asthma. Pulm Pharmacol Ther 2019;55:31–7. https://doi.org/10.1016/j.pupt.2019.01.005.

[11] Office of Dietary Supplements. Magnesium : Fact Sheet for Health Professionals 2019. https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/.
[12] Gourgoulianis KI, Chatziparasidis G, Chatziefthimiou A, Molyvdas PA. Magnesium as a relaxing factor of airway smooth muscles. J Aerosol Med 2001;14:301–7. https://doi.org/10.1089/089426801316970259.
[13] Cairns CB, Kraft M. Magnesium attenuates the neutrophil respiratory burst in adult asthmatic patients. Acad Emerg Med 1996;3:1093–7. https://doi.org/10.1111/j.1553-2712.1996.tb03366.x.
[14] Turner DL, Ford WR, Kidd EJ, Broadley KJ, Powell C. Effects of nebulised magnesium sulphate on inflammation and function of the guinea-pig airway. Eur J Pharmacol 2017;801:79–85. https://doi.org/10.1016/j.ejphar.2017.03.004.
[15] Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev 2017;11. https://doi.org/10.1002/14651858.CD003898.pub6.
[16] Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, et al. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. Lancet Respir Med 2013;1:301–8. https://doi.org/10.1016/S2213-2600(13)70037-7.
[17] Alansari K, Ahmed W, Davidson BL, Alamri M, Zakaria I, Alrifaai M. Nebulized magnesium for moderate and severe pediatric asthma: a randomized trial. Pediatr Pulmonol 2015;50:1191–9. https://doi.org/10.1002/ppul.23158.
[18] Schuh S, Sweeney J, Freedman SB, Coates AL, Johnson DW, Thompson G, et al. Magnesium nebulization utilization in management of pediatric asthma (MagNUM PA) trial: study protocol for a randomized controlled trial. Trials 2016;17:261. https://doi.org/10.1186/s13063-015-1151-x.
[19] Su Z, Li R, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children: a systematic review and meta-analysis. Pediatr Emerg Care 2018;34:390–5. https://doi.org/10.1097/PEC.0000000000000909.
[20] Mohammadzadeh Iraj, Mohammadi M, Khodabakhsh E. The effect of nebulised salbutamol plus magnesium sulfate in comparison with nebulised salbutamol plus normal saline in acute asthmatic attack in children. J Babol Univ Med Sci 2014;16:7–12.
[21] Sun YX, Gong CH, Liu S, Yuan XP, Yin LJ, Yan L, et al. Effect of inhaled MgSO4 on FEV1 and PEF in children with asthma induced by acetylcholine: a randomized controlled clinical trail of 330 cases. J Trop Pediatr 2014;60:141–7. https://doi.org/10.1093/tropej/fmt099.
[22] Wongwaree S, Daengsuwan T. Comparison efficacy of randomized nebulized magnesium sulfate and ipratropium bromide/fenoterol in children with moderate to severe asthma exacerbation. Asian Pacific J Allergy Immunol 2019. https://doi.org/10.12932/AP-190717-0118.
[23] Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J 2007;24:823–30. https://doi.org/10.1136/emj.2007.052050.
[24] Shan Z, Rong Y, Yang W, Wang D, Yao P, Xie J, et al. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. Respir Med 2013;107:321–30. https://doi.org/10.1016/j.rmed.2012.12.001.
[25] Griffiths B, Kew KM, Normansell R. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. Paediatr Respir Rev 2016;20:45–7. https://doi.org/10.1016/j.prrv.2016.07.001.
[26] Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. J Pediatr 1996;129:809–14. https://doi.org/10.1016/s0022-3476(96)70023-9.
[27] 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;34:389–97.
[28] Gürkan F, Haspolat K, Boşnak M, Dikici B, Derman O, Ece A. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children nonresponding to conventional therapy. Eur J Emerg Med 1999;6:201–5. https://doi.org/10.1097/00063110-199909000-00005.
[29] Scarfone RJ, Loiselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, et al. A randomized trial of magnesium in the emergency department treatment of children with asthma. Ann Emerg Med 2000;36:572–8. https://doi.org/10.1067/mem.2000.111060.
[30] Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. Arch Pediatr Adolesc Med 2000;154:979–83. https://doi.org/10.1001/archpedi.154.10.979.
[31] Torres S, Sticco N, Bosch JJ, Iolster T, Siaba A, Rocca Rivarola M, et al. Effectiveness of magnesium sulfate as initial treatment of acute severe asthma in children, conducted in a tertiary-level university hospital: a randomized, controlled trial. Arch Argent Pediatr 2012;110:291–6. https://doi.org/10.5546/aap.2012.291.
[32] Irazuzta JE, Chiriboga N. Magnesium sulfate infusion for acute asthma in the emergency department. J Pediatr (Rio J) 2017;93(Suppl 1):19–25. https://doi.org/10.1016/j.jped.2017.06.002.
[33] Goodacre S, Cohen J, Bradburn M, Stevens J, Gray A, Benger J, et al. The 3Mg trial: a randomised controlled trial of intravenous or nebulised magnesium sulphate versus placebo in adults with acute severe asthma. Health Technol Assess 2014;18:1–168. https://doi.org/10.3310/hta18220.