PGY-3

Critical Review Form
Meta-analysis

HYPERLINK "http://pmid.us/35616126"Ni H, Aye SZ, Naing C. Magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2022 May 26;5(5):CD013506.

Objectives: **"to assess the effects of magnesium sulfate for acute exacerbations of chronic obstructive pulmonary disease in adults." (p. 10)**

Methods: **This systematic review and meta-analysis sought to include randomized controlled trials with a parallel-group design that enrolled patients aged 35 years and older with acute exacerbations of COPD. The authors included full-text studies, abstracts, and unpublished data where available, and included trials with mixed COPD and asthma features and studies that recruited participants with other diseases, provided that outcomes for patients with COPD were available separately. Participants with pneumothorax, bronchiectasis, cystic fibrosis, and other chronic lung diseases or heart failure were excluded. Studies that compared magnesium sulfate administrations (irrespective of dose or route) as an adjunct to standard treatment for COPD were included.**

The primary outcomes were: 1) need for hospital admission form the ED; 2) need for non-invasive ventilation, assisted ventilation, or admission to the ICU; and 3) serious adverse events. Secondary outcomes included length of hospital or ED stay, all-cause mortality, adverse events, ABG measurements, lung function measurements, and symptom scores.

The authors searched multiple databases on August 2, 2021, including MEDLINE, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry, the Cochrane Airways Trials Register, and CENTRAL. The reference lists of all primary studies and review articles were also searched for additional references.

Out of 249 non-duplicate references, 207 were excluded, leaving 42 full-text articles for review. Of these, 11 studies met the included criteria and were included in this review. Only 10 of these were included in the quantitative synthesis (i.e. meta-analysis). These studies comprised 762 total participants with a mean age range from 62 to 76 years. All but one study included patients who presented to the ED, with one study including hospital inpatients. Seven studies evaluated the efficacy of IV magnesium sulfate, while 3 studies evaluated nebulized magnesium sulfate.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Guidelines recommend the use of IV magnesium sulfate in the management of moderate to severe asthma in both children and adults. While the pathophysiology of asthma and COPD are somewhat different, the potential benefits of smooth muscle relaxation, bronchodilation, and possible anti-inflammatory effects suggest a possible benefit in COPD as well.
2.	Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched multiple databases on August 2, 2021, including MEDLINE, Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry, the Cochrane Airways Trials Register, and CENTRAL. The reference lists of all primary studies and review articles were also searched for additional references.
3.	Were the primary studies of high methodological quality?	The included studies appear to be of overall moderate quality. Five of 11 studies were judged to be low risk of bias for random sequence generation, ten were reported to be "double blind" (though only 7 reported detailed processes of blinding), and 8 studies were at low risk of attrition bias. Three studies were at low risk of selective reporting bias while the others were at unclear risk. Two studies were at high risk of "other" bias as there were no full-text publications available.
4.	Were the quality assessments of the included studies reproducible?	Yes. Two review authors assessed risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions, which assesses risk of bias in the following domains: random sequence generation, allocation concealment, blinding or participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and "other bias."
II.	***What are the results?***	
1.	What are the overall results of the study?	IV magnesium vs. placebo or standard care: ● IV magnesium was associated with a reduction in the need for hospitalization (OR 0.45, 95% CI 0.23-0.88; I^2 = 0%) among 170 participants. NNT = 7. ● There was no significant difference in need for NIV and endotracheal intubation (OR 0.74, 95% CI 0.31-1.75; I^2 = 0%) among 52 participants. ● One trial reported no serious adverse events, but this was not reported in the other included trials. ● Magnesium was associated with a reduction in hospital length of stay (mean difference -2.7 days, 95% CI -4.73 to -0.66; I^2 = 0%). No study assessed ED length of stay.

		• No study reported all-cause mortality. • Two studies reported adverse events with none reported in the magnesium groups and 4 reported in the placebo group (flushing, nausea, weakness, dizziness, and increased secretions). • There was no significant difference in pooled results for changes in oxygen saturation (mean difference 0.32%, 95% CI -1.53% to 2.17%), FEV1 at 60 minutes (mean difference 0.0L, 95% CI -0.04 TO 0.05), FEV1 at 45 minutes (mean difference 2.10 mL, 95% CI -0.89 to 5.09), or change in peak expiratory flow rate. • There was a significant reduction in in dyspnea score with IV magnesium, with a mean difference of -1.40 (95% CI -1.83 to -0.96; I^2 = 0% for 101 participants).
2.	How precise are the results?	See above.
3.	Were the results similar from study to study?	Yes. I^2 values were 0% for all pooled analyses, suggesting a very low level of heterogeneity between studies. Visual analysis of the Forest plots supports this as well.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	The evidence suggests that use of IV magnesium in acute exacerbations of COPD is associated with a reduction in need for hospital admission (NNT = 7) and reduction in hospital length of stay. No adverse events were reported among patients receiving magnesium, though this was only reported in two studies.
2.	Were all patient important outcomes considered?	Mostly yes. The included studies assessed need for hospital admission, hospital length of stay, need for noninvasive mechanical ventilation and intubation, adverse events, dyspnea scores, and various phyiologic measures of respiratory function. They did not assess ED length of stay or patient satisfaction.
3.	Are the benefits worth the costs and potential risks?	Yes. IV magnesium, given in the doses used in these studies (1.2 to 2.4 grams) in patients without renal disease is quite safe and associated with a very low risk of adverse events. While the evidence in this review was graded low to very low according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework, this represents the best evidence available. Given the low risks associated with IV magnesium, this level of evidence is sufficient to change to practice.

Limitations:

1. **The quality of the included studies was low to moderate, based in large part on inadequate reporting of methodology.**
2. **The overall rating of the quality of evidence based on GRADE formatting was low to very low for the outcomes of interest.**
3. **Most of the pooled analyses included only one or two studies, hence a funnel plot was not performed to assess for publication bias.**

Bottom Line:

This systematic review and meta-analysis found that the use of IV magnesium for exacerbations of COPD was associated with a decreased need for hospital admission (OR 0.45, 95% CI 0.23-0.88), decreased hospital length of stay (mean difference -2.7 days, 95% CI -4.73 to -0.66), and low risk of adverse events. These findings receive low and very low Grades based on limited number of studies and poor reporting of methodology in the included studies.