MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

DRAFT PROTOCOL

Title:	**A systemic review and meta-analysis of the effects of inhaled corticosteroids in acute asthma treated in the emergency department**
Reviewers:	Dr. Nethmi Kearns, MRINZ Dr. James Harper, MRINZ Dr. Ingrid Maijers, MRINZ
Supervisor:	Professor Richard Beasley, MRINZ
Statistician:	Professor Mark Weatherall
Research Centre:	Medical Research Centre New Zealand (MRINZ)
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Funding sources:	Nil
Conflicts of interest:	None
Review question:	Is there evidence that inhaled corticosteroids alone compared to: inhaled corticosteroids and systemic steroids, systemic steroids alone, or inhaled placebo; have different outcomes in patients being treated for acute asthma in the Emergency department?
Background and Rationale:	The standard treatments for acute asthma in the Emergency Department (ED) are administration of beta$_2$-agonists and systemic steroids.[1,2] Oral and parenteral steroids reduce the risk of hospital admission in research participants with acute asthma especially in cases of severe exacerbation. [3,4] However, systemic steroid's adverse side effect profiles and relatively slow onset of actions means that it is clinically important to explore other methods of administration of anti-inflammatory agents. Inhaled steroids (ICS) compared to systemic steroids in acute exacerbations of asthma has been studied and ICS used in acute asthma attacks leads to reduced hospital admissions (OR 0.44; 95% CI 0.31 to 0.62; 12 studies; N = 960).[5] However, the effect of ICS when given <u>in addition</u> to systemic steroids uncertain. A systematic review and meta-analysis retrieving studies published to 2012 reported that research participants treated with ICS in addition to systemic corticosteroids compared to systemic steroids alone, had a reduced risk of hospital admission (OR 0.54; 95% CI 0.36 to 0.81; 5 studies; N = 433.)[5] However, even with the relatively small number of studies there was considerable

	heterogeneity, with the point estimate for I^2 of 52%.[5] The review's conclusion was that there was insufficient evidence that ICS therapy alone could be used either to replace or in addition to systemic steroids in acute asthma. The purpose of this review is to determine whether the use of inhaled corticosteroids (ICS) when administered either alone or in addition to systemic corticosteroids (SCS) leads to different clinical outcomes.	
Search strategy:	The literature search will use the following electronic bibliographic databases: PubMed, The Cochrane Library and clinicaltrials.gov. Studies published since 1960 in the English language will be retrieved. The search terms will be asthma AND (emergency or acute or severe or exacerbation or hospital or intensive or admit or admission or discharge) AND (steroid or corticosteroid or glucocorticoid or fluticasone or flovent or flixotide or beclomethasone or beclometasone or becloforte or becotide or QVAR or budesonide or pulmicort or flunisolide or aerobid or bronalide or triamcinolone or kenalog or beclovent or azmacort or vanceril or aerobec or ciclesonide or Alvesco) AND (inhale or nebulise or aerosol).	
Inclusion criteria:	**Population:**	Adults and children with acute exacerbation of asthma presenting to ED
	Intervention 1:	Participants receiving inhaled corticosteroids in addition to systemic corticosteroids
	Comparison 1:	Participants receiving inhaled placebo in addition to systemic corticosteroids
	Intervention 2:	Participants receiving inhaled corticosteroids
	Comparison 2:	Participants receiving systemic corticosteroids
	Intervention 3:	Participants receiving inhaled corticosteroids
	Comparison 3:	Participants receiving inhaled placebo
	Setting:	Emergency departments
	Study design:	Randomised Control Trials
Exclusion criteria:	Studies conducted on participants presenting to ED with mild asthma Studies published in a language other than English	
Outcome measures:	**Primary outcome:** Admission to hospital **Secondary outcomes:** 1. Pulmonary function tests (PEF and FEV_1) 2. Adverse effects	

	3. Physiological observations (Heart rate, Respiratory Rate, SpO2, Blood pressure) 4. Clinical symptom scores
Data Extraction:	Titles of studies retrieved using the search strategy will be screened by two independent reviewers to identify studies that may potentially meet the inclusion criteria. Abstracts for these titles will then be screened further to identify potential studies. The full text of these studies will be retrieved and independently assessed for eligibility by three reviewers. Any doubts or disagreement over the eligibility of studies will be resolved through discussion among the reviewers. Eligible studies will undergo data extraction. This will include study setting, study sample characteristics including demographic descriptors, recruitment details, details on the intervention and controls, outcomes and information for assessment of the risk of bias. The data will be extracted independently by two reviewers.
Risk of bias assessment:	Two reviewers will assess the risk of bias in each study. The characteristics that will be considered are random sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and any other source of bias. The Cochrane risk of bias tool will be utilised. Any difference in opinion will be resolved through discussion among the reviewer.
Data synthesis:	Meta-analysis of the risk of hospital admission will be by the inverse variance weighted method for odds ratios. We do not anticipate zero cell counts in the studies however if one or more study has zero cell counts then the Peto method will be used. Heterogeneity will be assessed by estimation of the I-square statistic, its confidence interval, and the associated Chi-square statistic. Should important heterogeneity be found then study-level characteristics that we have pre-specified will be where the trial participants were predominantly children or not; and whether the trial participants had mainly moderate or severe asthma. For continuous variables (PEF, FEV1) will be analysed by inverse variance weighting based on the mean effect and it variance using a small sample correction. Publication bias will be explored by funnel plots and a correlation coefficient for effect size versus variance.
Analysis of subgroups:	See meta-regression comments above.
References:	1. Beasley Richard, Hancox Robert J, Harwood Matire, Perrin Kyle, Poot Betty, Pilcher Janine, Reid Jim, Talemaitoga Api TD. Asthma and Respiratory Foundation NZ adult asthma guidelines: a quick reference guide. *N Z Med J*. 2016;129(1445). 2. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: A national clinical

guideline. 2016.

3. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane database Syst Rev*. 2001;(1):CD002178. doi:10.1002/14651858.CD002178

4. Rodrigo GJ. Rapid Effects of Inhaled Corticosteroids in Acute Asthma. *Chest*. 2006;130(5):1301-1311. doi:10.1378/chest.130.5.1301

5. Edmonds ML, Milan SJ, Camargo CA, Pollack C V, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane database Syst Rev*. 2012;12:CD002308. doi:10.1002/14651858.CD002308.pub2