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Increased versus Stable Dose of Inhaled Corticosteroids for Asthma Exacerbations: A Systematic Review and Meta-analysis

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Abstract:

Background: Increasing the dose of inhaled corticosteroids (ICS) is commonly used at early signs of loss of asthma control. However, the potential benefits and harms of this strategy remain unclear. We performed a systematic review and meta-analysis to compare increased dose with stable dose of ICS among adults and children with asthma.

METHODS: We searched Medline, EMBASE, and Cochrane Central Register of Controlled Trials from inception to August 02, 2018. Randomized clinical trials comparing increased doses vs stable doses of ICS for home management of asthma exacerbations in adults or children were included.

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RESULTS: The analyses included 8 trials totaling 3866 patients. Four trials were judged as low risk of bias, three were unclear risk, and one was ranked as high risk. Increased dose of ICS was associated with a significantly reduced risk of treatment failure compared with stable dose (OR 0.82, 95% CI 0.70-0.97, I²=6%; 314 (281 to 351) vs 358 events per 1,000 patients; moderate-quality evidence). There was no significant difference in unscheduled physician visits or hospital admission between increased or stable dose of ICS. However, increased dose of ICS increased the risk of non-serious adverse events (OR 3.50, 95% CI 1.93-6.35, I²=0%) but not serious adverse events.

CONCLUSIONS: Current evidence of moderate quality supports increasing the dose of ICS as part of a self-initiated action plan to reduce risk of requiring a course of systemic corticosteroids in people with an asthma exacerbation. However we did not find evidence for an impact on hospital admissions or unscheduled physician visits, and increased ICS dose increased risk of non-serious adverse events.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42018102769

KEYWORDS : asthma, pharmacology and pharmacogenomics, clinical immunology

Introduction

Asthma is one of the most common chronic diseases, with an estimated 300 million people affected worldwide.¹ Asthma exacerbations are frightening for patients, associated with considerable morbidity and mortality, and poses a considerable economic burden on the health care system.²⁻⁴

The daily use of inhaled corticosteroids (ICS) effectively controls the day-to-day asthma symptoms but have only partial efficacy in aborting exacerbations. Asthma guidelines recommend self-management plans for patients to manage their asthma but have been cautious to advocate for increasing the dose of ICS as part of the first steps in preventing or treating asthma exacerbations because of limited evidence.^{5,6} A previous Cochrane review also did not support increases in the dose of ICS to treat exacerbations in adults and children with asthma.⁷ However, this

review was limited by the small sample size and imprecisions. In recent months, two large randomized control trials (RCTs)^{8,9} were published. One of them⁹ was a landmark study discussing this topic, with a population size of 1922 patients dwarfing all the previous RCTs (a combined total of 1669). However, the two trials^{8,9} yielded different results.

Therefore, we thought it is important to conduct an updated systematic review and meta-analysis looking into the efficacy and safety of the increased vs stable dose of ICS as part of self-management plans to prevent exacerbations in children and adults with persistent asthma.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42018102769).¹⁰

Data sources and search strategy

Medline, EMBASE, the Cochrane Library at the CENTRAL Register of Controlled Trials were searched from the date of database inception until August 02, 2018. Moreover, ClinicalTrials.gov, European Union Clinical Trials Register, the Australian Research Council Longevity Intervention, and the World Health Organization International Clinical Trials Registry Platform were consulted for ongoing and completed trials. In addition, the references of RCTs, review articles and systematic reviews on the same topic were screened for eligible articles. No language or status restrictions were applied.

The following search terms were used alone or in combination: “corticosteroids”; “asthma”; “controlled trials”; “randomized controlled trial.”⁷ Details of the search strategy are presented in Supplement Table S1.

Study selection

Eligible studies met the following PICOS criteria:

- 1) Population: The population of interest included adults and children who were diagnosed with an asthma exacerbation. Asthma exacerbation was defined by guideline criteria such as those outlined in Global strategy for asthma management and prevention 2018,⁶ or by a pre-defined criteria in the included trials.
- 2) Intervention: increasing the daily dose of ICS as part of self-management plans for asthma exacerbations
- 3) Comparison intervention: a stable daily maintenance of ICS.
- 4) Outcome: 1 of the following outcomes:

Primary outcome was treatment failure (defined as asthma exacerbations requiring systemic corticosteroids).

Secondary outcomes were unscheduled acute care or emergency department visits or hospital admissions, unscheduled physician visits, serious adverse events, and non-serious adverse events. The serious adverse events and non-serious adverse events were defined by the included trials. The serious adverse events were usually defined as fatality, the need for hospitalization, prolongation of hospitalization, disability and study withdrawal due to the adverse event.

- 5) Study design: RCT (only parallel design).

Two independent investigators (YZ and JH) screened the titles and abstracts to determine if the citation met the eligibility criteria. They screened the full text of potentially relevant trials when both agreed that a citation met the eligibility criteria. Disagreements between the investigators were resolved by consensus, and if necessary, with consultation with a third investigator (FF). We contacted study authors to obtain missing information and unpublished data when needed to assess the inclusion criteria or when suitable data were not available.

Data collection process

Two independent investigators (YZ and JH) extracted data from the included trials into standardized collection forms and created tables for the evidence and outcomes. Disagreements between the two reviewers were resolved by consensus, and if necessary, consultation with a third investigator (FF).

Assessment of risk of bias and quality of evidence

Two independent investigators (YZ and JH) performed risk assessment using the Cochrane Collaboration risk of bias tool¹¹. The included RCTs were assessed for (1) random-sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) completeness of outcome data, (6) selective reporting, and (7) other sources of bias. Each domain was assessed as either low, unclear, or high risk of bias. We will consider the highest risk of bias for any criteria as the overall risk of bias for the study.

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework to rate the quality of evidence and generate absolute estimates of effect for each outcome.¹² The GRADE framework characterizes the certainty of a body of evidence based on study limitations, imprecision, inconsistency, indirectness, and other considerations.

Data synthesis

We used RevMan 5.3.3 software (a freeware available from The Cochrane Collaboration) to conduct all analyses. We used random effect models to estimate odds ratio (OR) with a corresponding 95% confidence interval (CI). A Mantel-Haenszel method was used to pool dichotomous data. A 2-tailed P value of < 0.05 was set for statistical significance. We assessed heterogeneity with the Chi^2 test and the I^2 test, with $I^2 > 50\%$ representing substantial.¹³

We conducted trial sequential analysis (TSA) to explore whether cumulative data were adequately powered to

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evaluate outcomes.¹⁴ An optimal information size set to a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), relative risk reduction of 20%, and the pooled control-group event rate across the included studies. TSA were conducted using Trial Sequential Analysis v.0.9.5.9 (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark)

We identified 2 variables for subgroup analyses based on the main controversies in the debate surrounding increased dose of ICS: dose and age. Differing opinions exist about the optimal dose of ICS. We stratified studies by dose of fold increase in baseline ICS dose into 2 categories: double vs quadruple). Because of the concern that the effect of increased dose of ICS may differ in children and adult, we stratified trials by age into 2 categories: child (age ≤ 13 years old) vs adult (age ≥ 18 years old). Both subgroups of children and adults may include adolescents (age from 13 to 18) when the results were not provided separately.

We planned sensitivity analyses by performing meta-analysis using alternative statistical methods (fixed-effect, risk ratios, and inverse variance) and adding the cross-over trials^{15,16} which have been excluded.

We planned to use a funnel plot to explore the possibility of publication bias when 10 or more trials were pooled.¹⁷

Results

Of 1333 screened records, 8 trials met the inclusion criteria (Figure 1).^{8,9,18-23} We excluded 11 trials (Supplement Table S2).²⁴⁻³⁴ The characters of the 8 trials randomizing 3866 patients are presented in Table 1. All trials were conducted in developed countries. Six trials were multicenter studies^{8,9,18,19,21,23}. Study sizes ranged widely (143-1922 patients), with 7 trials enrolling fewer than 500 patients and only 1 trial⁹ with more than 1500 patients. Four trials^{19-21,23} used the double dose of ICS as an interventional arm, whereas 4 trials^{8,9,18,22} used a quadruple or quintuple dose.

Risk of bias and quality of evidence

The risk of bias assessment for each included trial and the summative assessment by domain appear in Supplement Figure S1 and S2. Four trials were judged as low risk of bias, and three were unclear risk. Only one trial was ranked as high risk of bias because of unblinding of participants and personnel. The quality of evidence for all outcomes (summary of findings) is presented in Table 2.

Treatment failure

Treatment failure was reported in 7 trials. These trials reported 1235 treatment failure (increased ICS, 580/1821[31.9%]; stable ICS, 655/1829[35.8%]), and the increased dose of ICS was associated with a lower risk of treatment failure (OR 0.82, 95% CI 0.70-0.97, $I^2=6\%$, $P=0.02$, Figure 2). For treatment failure, TSA confirmed that the required information size for adults was met (Supplement Figures S3-4), but that for children was not (Supplement Figure S5). The funnel plot was not performed because less than 10 trials were included in the analysis.

We also performed subgroup analysis stratifying trials by age and size of dose increase. There was a reduced risk of treatment failure for adults (4 trials; OR 0.76, 95% CI 0.65-0.90; Figure 2) and with quadrupling of the dose (2 trials; OR 0.74, 95% CI 0.62-0.88; Supplement Figure S6); this benefit was not seen in children or double dose of ICS. However, these differences between subgroups were not statistically significant ($P=0.11$ and $P=0.24$, respectively)

The results of the sensitivity analyses, whereby all outcomes were reanalyzed using different methods did not change the overall findings (Supplement Table S3).

Unscheduled visits

Unscheduled acute care, emergency department visits, or hospital admissions were reported in 3 trials, and these were rare event in both groups. There was no statistically significant difference in the incidence of unscheduled acute care, emergency department visits, or hospital admission between the groups (OR 2.11, 95% CI 0.24-18.47, $I^2=49\%$, Supplement Figure S7).

Unscheduled physician visits were reported in 4 trials. Increased of ICS was not significantly associated with the incidence of unscheduled physician visits. (OR 0.85, 95% CI 0.61-1.18, $I^2=40\%$, Supplement Figure S8).

Adverse events

Compared with the stable dose of ICS, the increased dose of ICS was associated with the incidence of non-serious adverse events (OR 3.50, 95% CI 1.93-6.35, $I^2=0\%$; Supplement Figure S9) but not with risk of serious adverse events (OR 0.92, 95% CI 0.33-2.56, $I^2=62\%$; Supplement Figure S10).

Discussion

In this meta-analysis of 8 RCTs (including 3866 patients), we found that among patients with asthma who were treated with daily therapy with ICS, increasing the dose of ICS at the early stages of an asthma exacerbation significantly reduced the need for systemic corticosteroids. Subgroup analyses showed that the beneficial effect was seen in adults and with quadrupling the dose of ICS. However, these subgroup differences were not statistically significant. Sensitivity analyses showed similar results. This meta-analysis showed that the increased dose of ICS did not result in a significant decrease in unscheduled physician visits or hospital admission. Finally, this meta-analysis showed the increased dose of ICS was associated with the incidence of non-serious adverse events.

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Contrary to this study, a Cochrane review⁷ identifying 8 trials with a total of 1699 patients did not support the increase of dose of ICS as part of self-management plans to treat exacerbations in both adults and children with mild to moderate asthma, which was mainly limited by the wide confidence intervals for several outcomes. The Cochrane study differs from this study in several ways. First, the Cochrane study included all RCTs (2 crossover trials and 6 parallel trials). However, we only included RCTs with parallel design, because pooling trials with different designs might lead to heterogeneity. Second, we used a random instead of a fixed effect model to pool data because of substantial clinic heterogeneity among included trials. Third, this study included two recent large trials^{8,9}, which accounted for 56.2 % (2176/3866) of the total number of patients. These data reinforced our findings, provided improved precision concerning the treatment effects of increasing the dose of ICS, and allowed for meeting the minimum information size in TSA. Fourth and extremely important is that we identified two potentially practice-changing subgroup effect: this benefit was observed in adults (but not in children) and in patients using a quadruple dose of ICS (but not in patients using a double dose).

Strengths and limitations

Strengths of this meta-analysis include performing a comprehensive search; duplicate assessment of eligibility, risk of bias, and data abstraction; used a more conservative random effects model, and no restriction on language or time of publication for included trials. The meta-analysis also included rigorous assessment of the quality of evidence (and found the quality for primary outcome moderate), of the TSA (and met the minimum information size), of the credibility of subgroup analyses (and this benefit was shown in adults and in patients using a quadruple dose of ICS).

This study also has some limitations. First, as we pooled results from individual trials, this meta-analysis was limited by any flaws in the methodology of these trials. McKeever et al.'s study, the largest trial of this analysis which carried 57.5% of the weight of all trials combined, was an open-label trial.⁹ The open-label fashion may have introduced the bias attributed to knowing the intervention received, rather than the intervention itself,

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possibly affecting outcomes. Unbinding of patients and personnel also cannot ensure that the compared groups received a similar amount of attention and ancillary treatment.³⁵ Thus, the bias of McKeever et al.'s study may affect the quality of evidence of this meta-analysis, which resulted in downgrading from high to moderate in the GRADE assessment.

Second, the limited number of included trials limited the ability to detect publication bias. Studies presenting a positive, beneficial, effect have a higher chance of getting published, compared to those reporting negative findings. This situation may lead to publication bias. Thus, the possibility of publication bias might be low because all but one included trials had negative results.

Third, although there was no evidence of a significant difference between the groups concerning adverse events, this study might be not powered enough to assess adverse events. The increased dose of the ICS group may have a higher frequency of treatment-related adverse effects, such as oral candidiasis. But those were rare events in RCTs. As confidence bounds of those outcomes were too wide to rule out potentially important harms from the treatment of increased corticosteroids, caution is required when interpreting evidence of safety.

Clinical relevance

The Global Initiative for Asthma guideline (2018 update) recommends increasing ICS dose at the early signs of loss of asthma control in patients with persistent asthma receiving daily ICS.⁶ As the limited evidence for the guideline, our results may strengthen it. The asthma world is reasonably convinced that doubling the dose of ICS is ineffective.⁷ Quadrupling the dose of inhaled glucocorticoids was identified in the subgroup analyses as an efficacious intervention. With regards to the applicability of the findings, most data were derived from adults. Study results may not apply to children, as just three included trials^{8,21,23} totaling 648 individuals, which did not meet the optimum size.

Conclusions

In this systematic review and meta-analysis of patients with asthma exacerbation, the use of the increased versus stable ICS dose reduces the odds of requiring systemic corticosteroids for the exacerbation. However, we did not find evidence for an impact on hospital admissions or unscheduled physician visits, and increased ICS dose increased risk of non-serious adverse events.

Author contributions:

FF conceived the study and designed the protocol.

JH and YZ performed the literature search.

JH and YZ selected the studies.

JH and YZ extracted the relevant information.

JH and FF synthesized the data.

FF wrote the first draft of the paper.

FF, YZ, JH, YY, and AF critically revised successive drafts of the paper and approved the final version.

FF are the guarantors of the study.

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Competing interests: None

Acknowledgments: None

Ethical approval: Not required

Data Sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure descriptions:

Figure 1 Flow diagram of the Literature Search

Figure 2 Forest plot of comparison of increased vs. stable doses of inhaled corticosteroids, outcome treatment failure-need for systemic corticosteroids

Table 1. The characters of included trials

Author	Year	No of patients	No of site	Country	Age range	Mean age	Maintenance dose of ICS	Increase d dose of ICS	Follow-up
Foresi	2000	213	14	Italy	18-65	39	Budesonide 100 mcg BID	quintuple dose	6-month
Fitzgerald	2004	290	4	Canada	>13	32	Budesonide 100, 200 or 400 mcg BID (Mean 635 mcg/d BDP)	double dose	6-month
Harrison	2004	390	1	UK	>16	50, 48	Usual ICS dose (mean 710 mcg/d BDP)	double dose	12-month
Wainwright	2009	251	8	Australia	3-14	Unclear	Fluticasone 125 mcg/d or usual higher dose	double dose	12-month
Oborne	2009	403	1	UK	>16	53, 55	Usual ICS dose (mean 520 mcg/d BDP)	quadruple dose	12-month
Martinez	2011	143	5	USA	6-18	11.4	Beclomethasone 40 mcg BID	double dose	44-week
Jackson	2018	254	17	USA	5-11	8.0	Fluticasone 88 mcg BID	quintuple dose	48-week
McKeever	2018	1922	24	UK	>16	56.2, 56.7	Median 800 mcg/d BDP	quadruple dose	12-month

ICS: inhaled corticosteroids;

BID: Twice A Day (Latin: Bis In Die) ;

BDP: beclomethasone or equivalent.

Table 2 GRADE evidence profile of all outcomes

Outcome	No. of patients (Studies)	Relative effect (95% CI)	I ²	Illustrative comparative risks (95% CI)		Quality of the evidence (GRADE)
				Assumed risk	Corresponding risk	
				Stable ICS	Increase ICS	
Primary outcome						
Exacerbation requiring systemic corticosteroids	3650 (7)	OR 0.82 (0.7 to 0.97)	6%	358 per 1000	314 per 1000 (281 to 351)	Moderate ¹
Subgroup: Children	648 (3)	OR 1.05 (0.73 to 1.51)	11%	347 per 1000	316 per 1000 (267 to 371)	Moderate ²
Adults	3002 (4)	OR 0.76 (0.65 to 0.9)	0%	371 per 1000	310 per 1000 (277 to 347)	Moderate ¹
Subgroup: Double dose	1074 (4)	OR 0.91 (0.67 to 1.25)	0%	207 per 1000	192 per 1000 (149 to 246)	Moderate ²
Quadruple dose	2322 (2)	OR 0.74 (0.62 to 0.88)	0%	442 per 1000	370 per 1000 (329 to 411)	Moderate ¹
Secondary outcome						
Unscheduled acute care, ED visit or hospital admission	648 (3)	OR 0.47 (0.06 to 3.85)	47%	25 per 1000	12 per 1000 (2 to 90)	Moderate ²
Unscheduled physician visits	2753 (4)	OR 0.85 (0.61 to 1.18)	43%	313 per 1000	279 per 1000 (217 to 350)	Moderate ²
Serious adverse events	2316 (3)	OR 0.92 (0.33 to 2.56)	62%	29 per 1000	27 per 1000 (10 to 71)	Low ^{2,3}
Non-serious adverse events	2064 (3)	OR 1.06 (0.48 to 2.34)	36%	65 per 1000	69 per 1000 (32 to 140)	Moderate ²

CI: Confidence interval; **OR:** Odds ratio;

Treatment failure was defined as treatment with systemic glucocorticoids or an unscheduled health care consultation for asthma.

GRADE Working Group grades of evidence

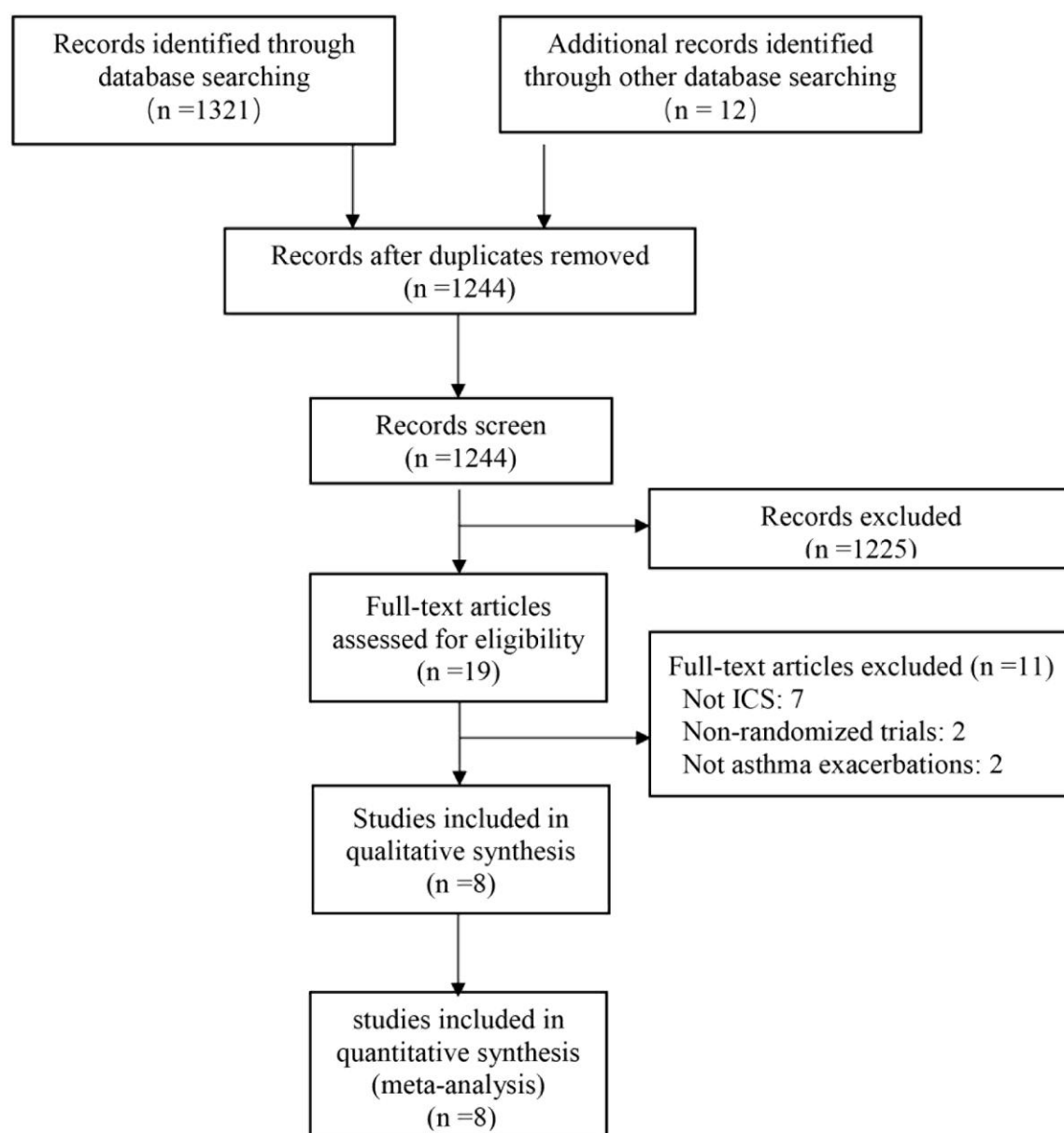
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

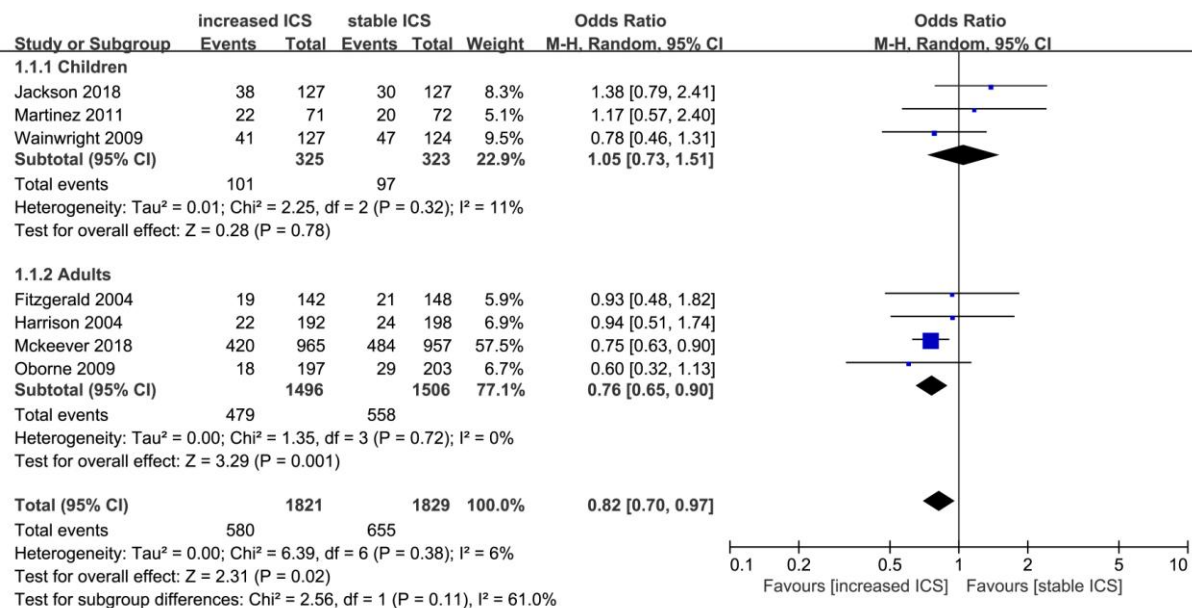
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ the largest trial was not double-blind ² imprecisions ³ inconsistency





Supplemental e-material

Table S1: Literature search strategy

Table S2: List of excluded trials and reasons for exclusion

Table S3: sensitivity analyses for the primary outcomes

Figure S1: Risk of bias summary

Figure S2: Risk of bias graph

Figure S3: Trial sequential analysis of treatment failure for children and adults

Figure S4: Trial sequential analysis of treatment failure for adults

Figure S5: Trial sequential analysis of treatment failure for children

Figure S6: Subgroup analysis for treatment failure –based on increased dose

Figure S7: Forest plot of unscheduled acute care, emergency department visits, or hospital admission

Figure S8: Forest plot of unscheduled physicians visits

Figure S9: Forest plot of non-serious adverse events

Figure S10: Forest plot of serious adverse events

Supplement Table S1 Literature search strategy:

Database	Search strategy
PubMed	1. exp steroid/ 2. exp corticosteroid/ 3. (steroid* or glucocorticoid* or corticosteroid* or cortisone* or bronchoconstrict* or fluticasone * or beclomethasone*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. 1 or 2 or 3 5. exp Asthma/ 6. (asthma\$ or antiasthma\$ or anti-asthma\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 7. 5 or 6 8. ((randomized controlled trial or controlled clinical trial). pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh. 9. 4 and 7 and 8
Cochrane Central	#1 MeSH descriptor: [Asthma] explode all trees #2 MeSH descriptor [antiasthma, anti-asthma] explode all trees #3 #1 or #2 #4 (steroid* or glucocorticoid* or corticosteroid* or cortisone* or hydrocortisone* or bronchoconstrict* or fluticasone * or beclomethasone*) #5 #3 and #4
Embase	1. exp steroid/ 2. (corticosteroid* or steroid*). ti,ab. 3. (steroid* or glucocorticoid* or corticosteroid* or cortisone* or bronchoconstrict* or fluticasone * or beclomethasone*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 4. 1 or 2 or 3 5. exp asthma / 6. exp antiasthma/

	7. (antiasthma or anti-asthma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 8. 5 or 6 or 7 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 4 and 8 and 9
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Supplement Table S2 List of excluded trials and reasons for exclusion

Trial	Reason for exclusion
Bullard 1996 ¹	Not asthma
Connett 1993 ²	Not use of ICS as the control arm
Currie 2003 ³	Not exacerbations
De Benedictis 2005 ⁴	Not use of ICS as the control arm
Gillbert 2018 ⁵	Not a trial
Hedlin 1999 ⁶	Not use of ICS as the control arm
Lee-Wong 2002 ⁷	Not use of ICS as the control arm
Rabe 2006 ⁸	Not use of ICS as the control arm
Roberts 2018 ⁹	Not a trial
Sobieraj 2018 ¹⁰	Not use of ICS as the control arm
Yousef 2012 ¹¹	Not stable ICS arm

ICS: inhaled corticosteroids

Supplement Table S3. sensitivity analyses for the primary outcomes

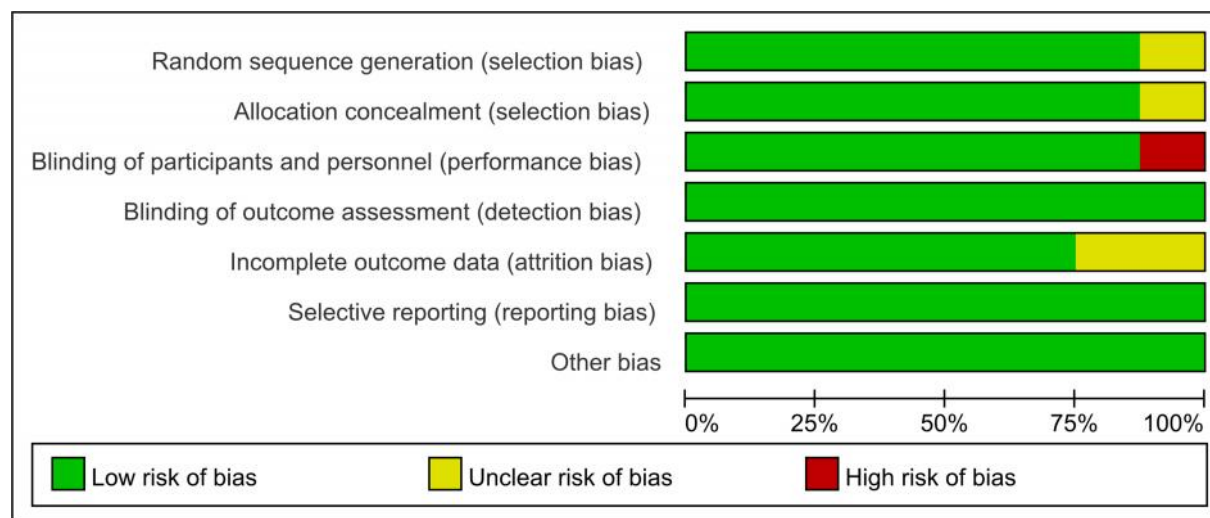
	OR (95%CI)	I ²
reweighing trials using risk ratios	0.88 [0.81, 0.96]	0%
reweighing trials using fixed-effect	0.81 [0.70, 0.94]	6%
reweighing trials using inverse variance	0.81 [0.70, 0.94]	8%
reweighing trials using adding the cross-over trials	0.81 [0.70, 0.94]	0%

OR: odds ratio

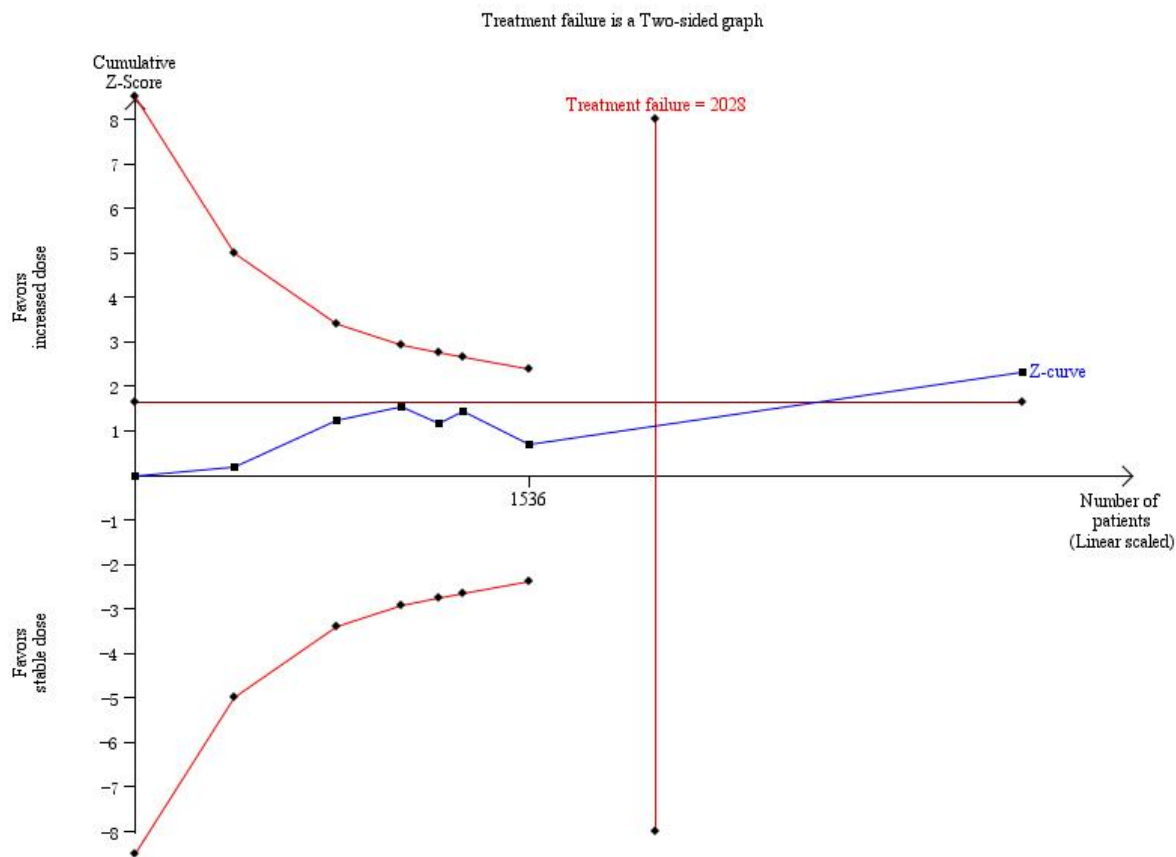
Supplement Figure S1: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fitzgerald 2004							
Foresi 2000							
Harrison 2004							
Jackson 2018							
Martinez 2011							
Mckeever 2018							
Oborne 2009							
Wainwright 2009							

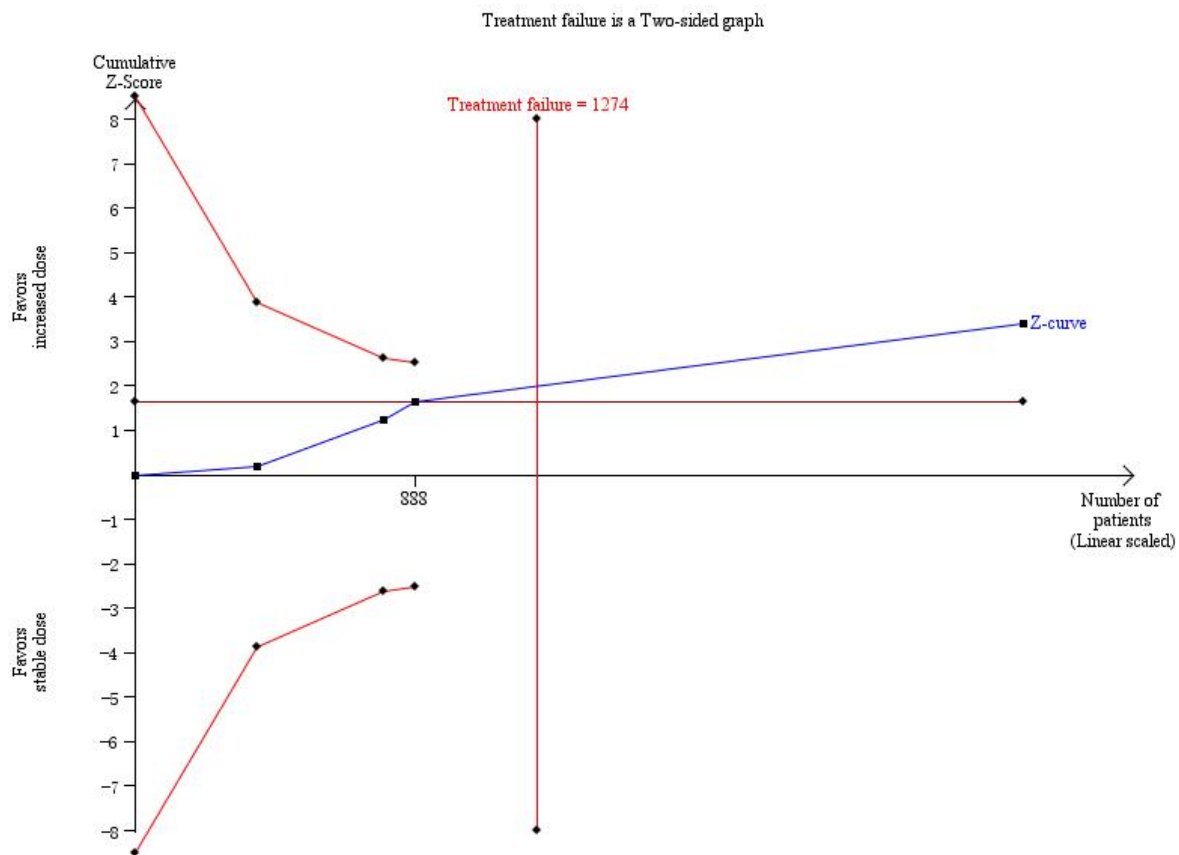
Supplement Figure S2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



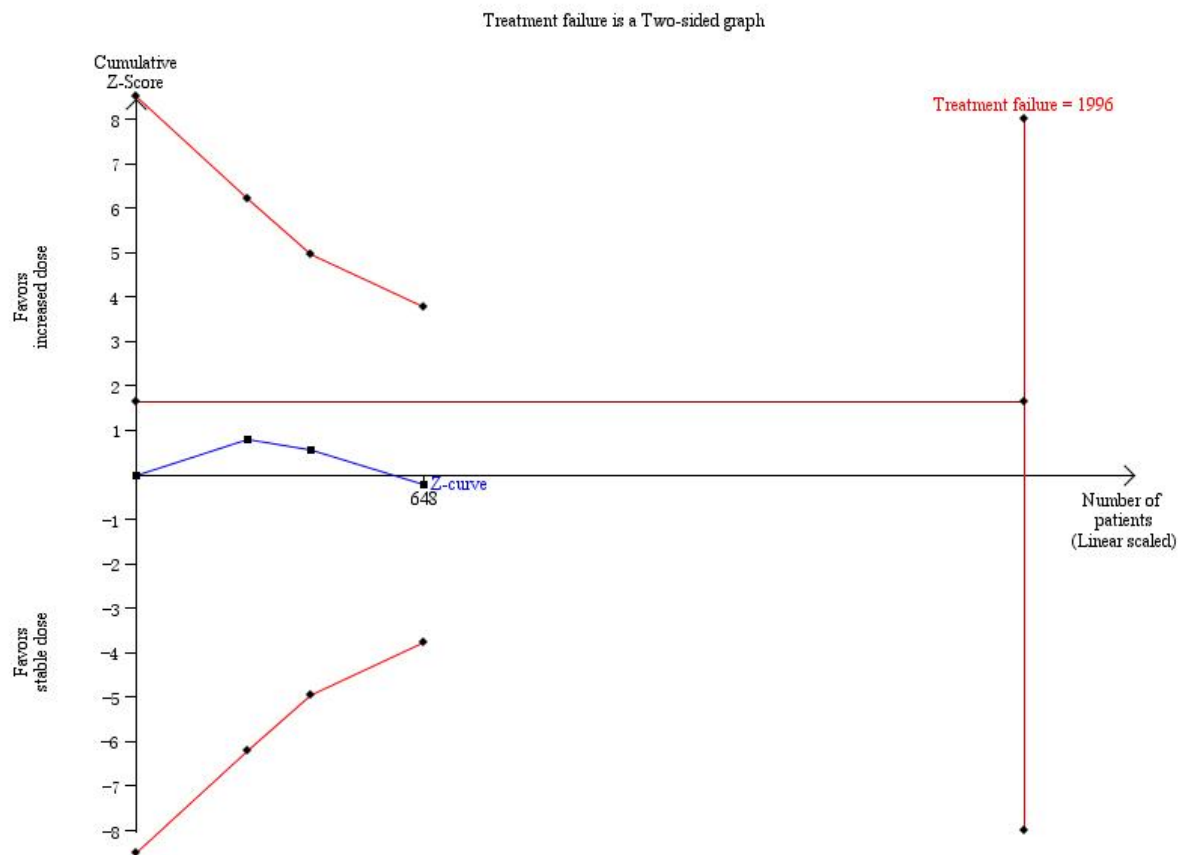
Supplement Figure S3. Trial sequential analysis of treatment failure for adults and children.



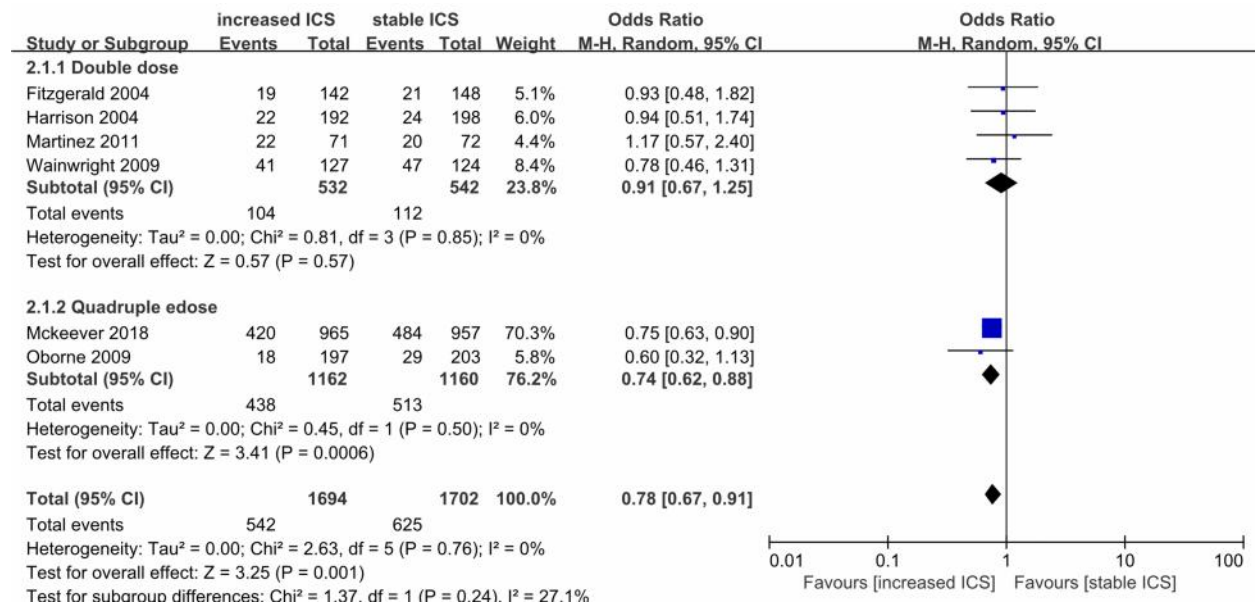
Supplement Figure S4. Trial sequential analysis of treatment failure for adults



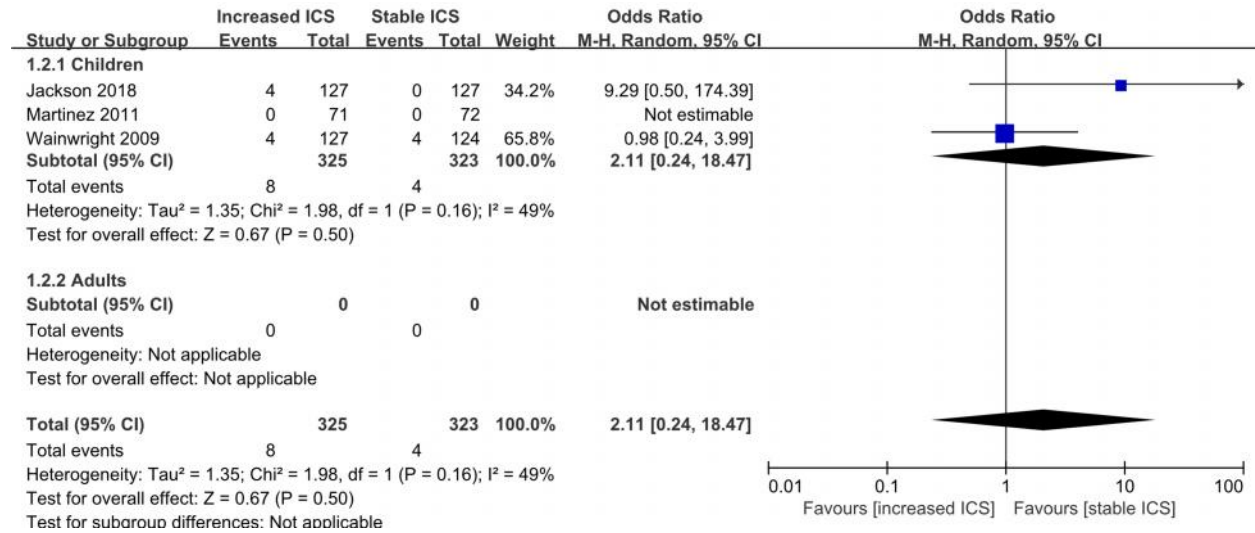
Supplement Figure S5. Trial sequential analysis of treatment failure for children



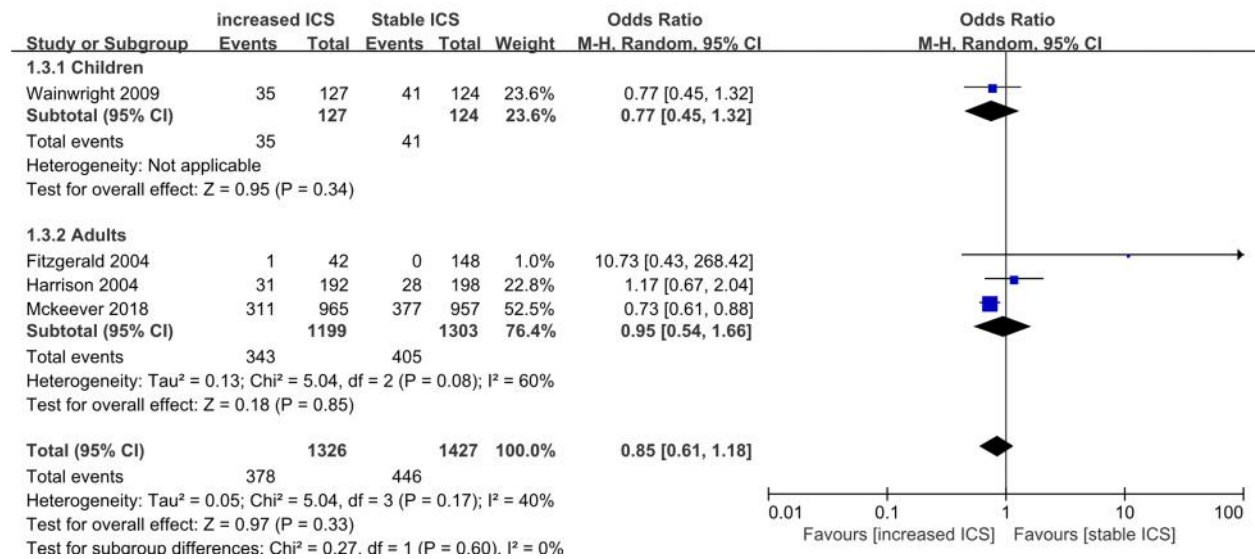
Supplement Figure S6. Subgroup analysis for treatment failure –based on increased dose. df = degrees of freedom, M-H = Mantel-Haenszel.



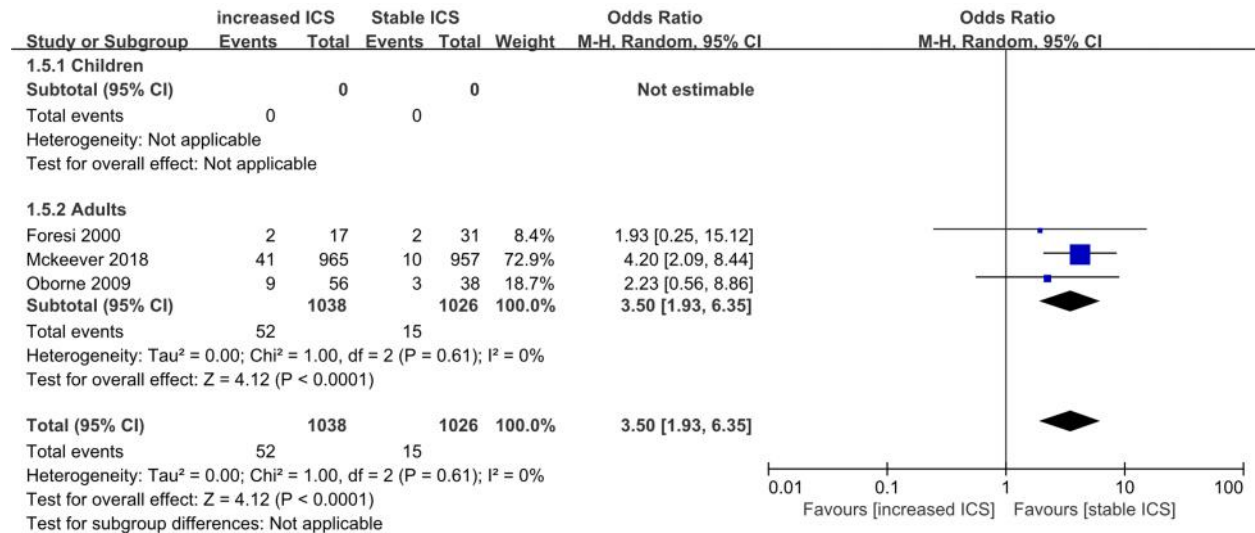
Supplement Figure S7 Forest plot of unscheduled acute care, emergency department visits, or hospital admission. df = degrees of freedom, M-H = Mantel-Haenszel.



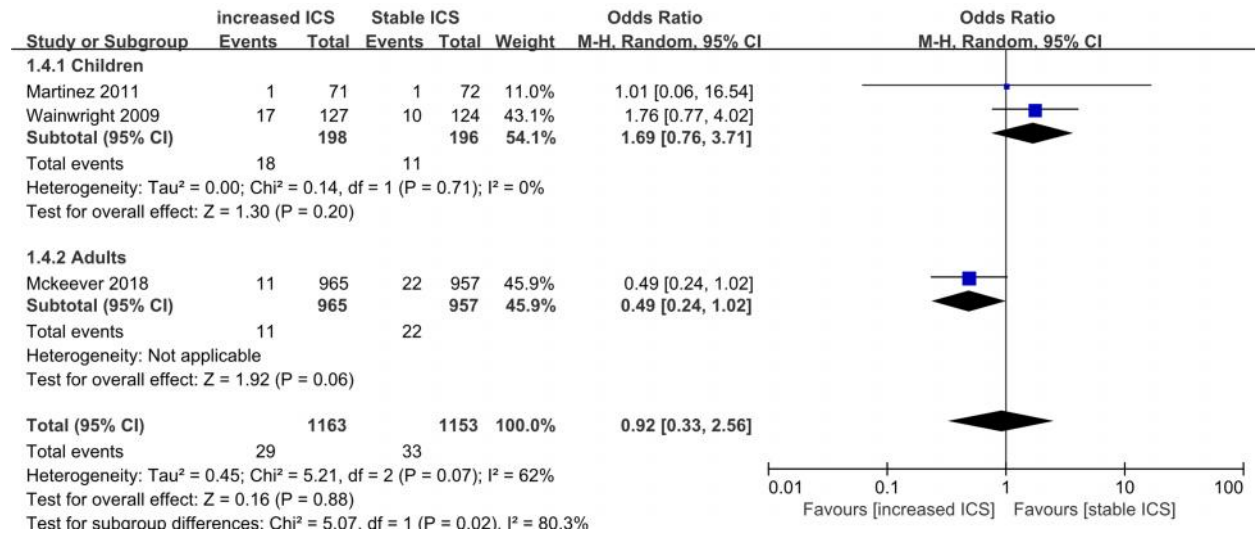
Supplement Figure S8: Forest plot of unscheduled physicians visits. df = degrees of freedom, M-H = Mantel-Haenszel.



Supplement Figure S9: Forest plot of non-serious adverse events. df = degrees of freedom, M-H = Mantel-Haenszel.



Supplement Figure S10: Forest plot of serious adverse events. df = degrees of freedom, M-H = Mantel-Haenszel.



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