Inhaled *versus* systemic corticosteroids for acute exacerbations of COPD: a systematic review and meta-analysis

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Abstract

This meta-analysis compares the efficacy and safety of inhaled *versus* systemic corticosteroids for COPD exacerbations.

Following a pre-registered protocol, we appraised eligible randomised controlled trials (RCTs) according to Cochrane methodology, performed random-effects meta-analyses for all outcomes prioritised in the European Respiratory Society COPD core outcome set and rated the certainty of evidence as per Grading of Recommendations Assessment, Development and Evaluation methodology.

We included 20 RCTs totalling 2140 participants with moderate or severe exacerbations. All trials were at high risk of methodological bias. Low-certainty evidence did not reveal significant differences between inhaled and systemic corticosteroids for treatment failure rate (relative risk 1.75, 95% CI 0.76–4.02, n=569 participants); breathlessness (mean change: standardised mean difference (SMD) −0.11, 95% CI −0.36–0.15, n=239; post-treatment scores: SMD −0.18, 95% CI −0.41–0.05, n=293); serious adverse events (relative risk 1.47, 95% CI 0.56–3.88, n=246); or any other efficacy outcomes. Moderate-certainty evidence implied a tendency for fewer adverse events with inhaled compared to systemic corticosteroids (relative risk 0.80, 95% CI 0.64–1.0, n=480). Hyperglycaemia and oral fungal infections were observed more frequently with systemic and inhaled corticosteroids, respectively.

Limited available evidence suggests potential noninferiority of inhaled to systemic corticosteroids in COPD exacerbations. Appropriately designed and powered RCTs are warranted to confirm these findings.

Introduction

According to the World Health Organization, COPD ranks as the third leading cause of death [1]. Along the disease course, exacerbations impose a substantial burden on health-related quality of life, disease progression, morbidity and mortality [2]. Although the initial triggering factor and the underlying pathophysiology vary considerably, ~20–40% of patients present enhanced airway eosinophilic inflammation that responds well to systemic corticosteroids [3–5]. Current treatment guidelines recommend systemic corticosteroids administration for severe COPD exacerbations or those characterised by increased breathlessness [6–9].

Indeed, systemic corticosteroids improve exacerbation outcomes, including treatment failure and length of hospital stay, and prevent exacerbation relapse by 1 month [10, 11]. However, they can induce numerous

well-known side-effects [12–18]. Even short regimens have been associated with severe adverse events, such as pneumonia, sepsis and death [19, 20]. This necessitates novel treatment strategies to improve the benefit-to-risk ratio. Systemic corticosteroids adverse effects can be particularly detrimental for COPD patients, who commonly suffer from other chronic diseases, such as heart failure, diabetes mellitus and muscle weakness [21, 22]. A high cumulative corticosteroid dose usually precedes the occurrence of adverse effects [23], which renders patients with frequent exacerbations more susceptible [24].

In contrast, inhaled corticosteroids exert local anti-inflammatory effects with little systemic activity [25]. Therefore, they may improve exacerbation outcomes with less adverse events, potentially posing a more favourable benefit-to-risk ratio than systemic corticosteroids. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report has acknowledged nebulised budesonide as a potential alternative to intravenous methylprednisolone for exacerbations, based on four randomised controlled trials (RCTs) [9, 26].

We conducted a systematic review and meta-analysis to compile and appraise RCTs that compared the safety and clinical efficacy of inhaled *versus* systemic corticosteroids for the treatment of moderate and severe COPD exacerbations.

Methods

The protocol for this systematic review and meta-analysis was prospectively registered with PROSPERO (identifier CRD42021284297) [27]. We complied with the methodology recommended by the Cochrane Collaboration [28] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [29] and present our report according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30].

Eligibility criteria

We included randomised and quasi-randomised studies comparing the efficacy and safety of inhaled to systemic corticosteroids in adults with moderate or severe COPD exacerbations. COPD exacerbation was defined based on clinical diagnosis. Patients with a primary presenting diagnosis other than COPD exacerbation were excluded. Systemic administration was acceptable *via* oral and intravenous routes and inhaled delivery *via* nebulisers and inhaler devices. Normal saline nebulisation was acceptable as placebo for blinding purposes.

Outcome measures

We evaluated all clinically important outcomes that have been prioritised in the European Respiratory Society (ERS) COPD Exacerbations core outcome set [31] and further secondary outcomes relevant to the intervention. Specifically, the primary outcomes were treatment success (namely a dichotomous measure of the overall outcome of the exacerbation according to clinicians' judgement and/or assessment of symptoms and signs [32]); breathlessness; and serious adverse events. Secondary outcomes included health-related quality of life; overall symptom score, cough and sputum production; hospitalisation duration; indication for higher level of care, *i.e.* admission to the hospital, implementation of invasive or noninvasive mechanical ventilation, or admission to the intensive care unit (ICU) for the presenting exacerbation; future exacerbations and future hospital admissions; mortality; total adverse events; hyperglycaemia; fungal infection; levels of oxygen and carbon dioxide in the arterial blood and oxygen saturation; disease progression assessed by pulmonary function tests, *i.e.* forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC); activities of daily living; worsening of symptoms after treatment initiation; development of resistant bacteria; development of pneumonia; and treatment adherence.

Search strategy, study selection and data abstraction

Using a structured search strategy, we searched MEDLINE/PubMed, the Cochrane Central Register of Controlled Trials and the conference proceedings of the ERS, American Thoracic Society and Asian Pacific Society of Respirology, up to 16 November 2023, with no language or time restrictions. Two authors independently screened all studies retrieved at a title/abstract level, the reference lists of all relevant studies, and further assessed the full text of all potentially eligible studies for inclusion. We extracted relevant data from eligible studies regarding the trials' design, participants' baseline characteristics, interventions, and pre-specified outcomes in duplicate in a piloted Excel spreadsheet. Any disagreements between the two independent authors were resolved through discussion or adjudication by a third reviewer.

Risk of bias and certainty of evidence assessment

Risk of bias at the study level was determined according to the Cochrane Risk of Bias Tool v2 (RoB2) [33, 34]. We assessed the certainty of the body of evidence per outcome according to GRADE

methodology [35, 36], considering the risk of bias, imprecision, inconsistency, indirectness and publication bias. We could not assess the latter using funnel plots, since all our meta-analyses involved <10 trials. However, we searched conference proceedings and trial registers to eliminate potential bias.

Data synthesis

We used Review Manager 5.4.1 (Cochrane) to perform random-effects meta-analyses anticipating significant clinical and methodological heterogeneity. We calculated mean differences (MD) and relative risks as effect estimates for continuous and dichotomous data, respectively. When it was meaningful, we used standardised mean differences (SMD), dividing the intervention effect by the corresponding standard deviation of each study, for continuous data reported using variable instruments assessing the same outcome. Effect estimates are presented along with their 95% confidence intervals and I^2 as a measure of heterogeneity. We explored significant heterogeneity in pre-specified sensitivity and subgroup analyses. Outcomes were assessed post-treatment and at long-term (>4 weeks) follow-up time points. Secondary analyses were performed at time points up to 7 days and beyond 7 days.

Sensitivity and subgroup analyses

Subgroup analyses were performed according to exacerbation severity, aetiology, and inhaled corticosteroids daily dose.

In sensitivity analyses we repeated the meta-analyses using the fixed-effect model. Moreover, we only included studies that explicitly excluded patients with asthma, patients with <10 pack-years smoking index and patients who might have received corticosteroids prior to recruitment. A sensitivity analysis of studies reporting high treatment adherence (>85%) was planned, but not performed due to insufficient data.

Results

Study selection and baseline characteristics

The search strategy and the study selection process are described in the PRISMA flowchart (supplementary figure A1). We included 18 randomised and two [37, 38] quasi-randomised controlled trials with 2140 participants that fulfilled the eligibility criteria (table 1 and supplementary table A1).

Most trials (n=14) recruited hospitalised participants. Outpatient [54] and emergency department [39] settings were each evaluated in one trial. Clinical setting was not clarified in the remaining four trials. Blinding was double in six trials and single in four trials, whereas another one was open-labelled and nine did not report on blinding. Concomitant asthma was explicitly excluded in most trials (n=14). Eight trials excluded participants with a smoking index <10 pack-years [53, 54, 58] or <20 pack-years [42, 47, 48, 50, 56]. We noted no significant baseline differences between treatment arms, apart from two trials [48, 58] (supplementary table A1). Participants were followed-up for a median 10 days, with a range from 24 h [39] to 12 months [41].

Duration of exacerbation symptoms prior to enrolment was generally not specified, apart from three trials [47, 50, 64] with a mean duration ranging between 2.4 and 11 days. Four trials set an upper limit of 24 h [53], 7 days [43, 54] or 14 days [50] of symptoms. Exacerbations were not specifically eosinophilic, but rather unselected; one trial [56] recruited exclusively patients with infective bacterial exacerbation. Participants had not received corticosteroids for the presenting exacerbation in 16 trials, five of which explicitly excluded both systemic and high-dose inhaled corticosteroids (table 1). Another trial [54] prohibited high-dose inhaled corticosteroids at study entry, but all participants had received oral corticosteroids prior to randomisation as ambulatory treatment for the exacerbation. Withdrawal rates were high or imbalanced in six trials, up to 29.3% for inhaled [66] and up to 24.5% for systemic corticosteroids [45], being >10% higher for inhaled than systemic corticosteroid arms in two trials [50, 66].

Corticosteroids were administered for a median of 7 days, ranging from 1 to 15 days (table 1). The inhaled corticosteroids arms received budesonide mostly *via* a nebuliser (n=17 trials, median dose 8 mg·day^{-1}, range 1.5–8 mg·day^{-1}) or *via* inhaler devices (n=2, dose 800–1280 μg·day^{-1}), but one trial used both in different arms [53]. Two other trials [45, 50] initially administered corticosteroids *via* a nebuliser, and afterwards *via* an inhaler device. Systemic corticosteroids, namely prednisone, prednisolone, methylprednisolone and hydrocortisone, were administered at various dosages consistent with routine clinical practice, intravenously (n=8), orally (n=6), both (in different treatment arms, n=3) [57, 59, 61] or allowed either (n=1) [38]. Two trials [45, 56] initially offered intravenous and later oral corticosteroids. Concurrent treatment for the exacerbation included bronchodilators with or without methylxanthines, antibiotics, mucolytics, antitussives, oxygen supplementation, fluid and electrolyte support.

TABLE 1 Characteristics of the included trials

First author [ref.], registry identifier	Study design	Participants n (withdrawn %)	Age years mean±SD	Male %	Inclusion diagnosis	Asthma	SCS/ICS (previous month)	Regimen
Aghili [39] IRCT20180523039800N1	RCT, DB, ED	84 (0)	65.3±10.4	78.6	Moderate to severe AECOPD in patients aged >18 years with COPD as per ATS/ERS [40] Excluded comorbidities (diabetes mellitus, hypertension), indication for invasive MV	No	No/no	Nebulised budesonide 1.5 mg (3 doses per 30 min) *versus* p.o. prednisolone 50 mg once
Ding [41]	RCT, SB, inpatient	471 (3.2)	73.4±8.6	80.9	Clinical AECOPD in patients aged 60–80 years previously diagnosed with COPD Excluded invasive MV, diabetes, systemic diseases requiring hospitalisation, AECOPD within 1 month	No	No/allowed stable	Nebulised budesonide 6 mg·day^{-1} three times daily *versus* i.v. methylprednisolone 40 mg once daily for 7 days
Djordjevic [42]	RCT, DB, inpatient	60 (NI)	69.1±NI	68.3[#]	AECOPD in patients aged >50 years with smoking history; >20 years and breathlessness on exertion for 3 years	NI	Not recently[¶]	Nebulised budesonide 8 mg·day^{-1} four times daily *versus* p.o. prednisolone 30 mg·day^{-1} once daily for 7 days
Gong [43]	RCT, SB, inpatient	53[+] (8.9)[#]	61.9±NI	83	Moderate or severe AECOPD as per the Chinese Medical Association guidelines [44] within 7 days Excluded other causes, systemic disease (renal, hepatic insufficiency, heart disease), indication for MV	NI	Not for 24 h[¶]	Nebulised budesonide 3 mg·day^{-1} three times daily *versus* i.v. methylprednisolone 40 mg·day^{-1} once daily for ⩾7 days
Gunen [45] NCT00274222	RCT, SB,[§] inpatient	106 (22.6)	64.4±8.5	82.9	Severe AECOPD (clinical criteria) in patients with COPD (ATS [46]) Excluded specific causes for exacerbation requiring hospitalisation (*e.g.* congestive heart failure); indication for MV or ICU; AECOPD within 1 month	NI	No/NI	Nebulised budesonide 6 mg·day^{-1} four times daily *versus* i.v. prednisolone 40 mg once daily for 15 days If discharged on day 11–15: inhaled budesonide *versus* p.o. methylprednisolone 32 mg once daily up to day 15
Kafee [47]	RCT, SB, inpatient	100 (10)	61.4±NI	86.7	Clinical AECOPD confirmed with spirometry in patients aged >40 years with SI ⩾20 pack-years Excluded specific causes, *e.g.* heart failure, imminent acute respiratory failure AECOPD for 11±2.7 days prior to recruitment	No	No/no[f]	Nebulised budesonide 2 mg·day^{-1} twice daily *versus* p.o. prednisolone 40 mg·day^{-1} once daily (NI on duration)
Liu [37]	Quasi-RCT, NI, NI	82 (NI)	73.9±11.2	68.3	AECOPD with FEV$_1$ 25–60% predicted Excluded severe heart, renal, liver insufficiency, diabetes mellitus and severe respiratory failure	No	No/NI	Nebulised budesonide 4 mg·day^{-1} twice daily oxygen-driven *versus* i.v. methylprednisolone 40 mg·day^{-1} (NI on duration)

Continued

TABLE 1 Continued								
First author [ref.], registry identifier	Study design	Participants n (withdrawn %)	Age years mean±SD	Male %	Inclusion diagnosis	Asthma	SCS/ICS (previous month)	Regimen
MAKAROVA [48]	RCT, OL, inpatient	78 (0)	63.7±10.4	65.4	Clinical AECOPD in patients aged >40 years with SI ⩾20 pack-years previously diagnosed with COPD (GOLD [49]) Excluded MV and ICU, oncological pathology, autoimmune diseases, heart failure class III–IV NYHA and respiratory infection/antibiotics ⩽1 month prior	No	No/NI	Nebulised budesonide 4 mg·day^{-1} twice daily versus i.v. prednisolone 120–180 mg·day^{-1} for 7–14 days
MALTAIS [50]	RCT, DB, inpatient	133 (22.6)	69.7±8.2	81.9	Clinical AECOPD with increased breathlessness ⩽2 weeks in patients aged >50 years with SI ⩾20 pack-years and COPD (ATS [46]) When available (69%#), baseline post-bronchodilation FEV$_1$ <70% predicted and FEV$_1$/FVC <70% Excluded indication for MV or ICU; specific cause (e.g. heart failure) AECOPD for 6.1±3.9 days prior to recruitment	No	No/no## (recently)	Nebulised budesonide 8 mg·day^{-1} four times daily for 72 h followed by inhaled budesonide 2000 μg·day^{-1} for 7 days versus p.o. prednisolone 60 mg·day^{-1} twice daily for 72 h followed by 40 mg·day^{-1} for 7 days
MIRICI [51]	RCT, DB, inpatient	44 (9.1)	63.9±NI	72.5	Clinical criteria for moderate or severe AECOPD (Turkish national [52]) in patients previously diagnosed with COPD as per ATS [46] with spirometry Excluded systemic diseases (e.g. diabetes mellitus, hypertension), indication for MV	No	No/NI	Nebulised budesonide 8 mg·day^{-1} twice daily versus i.v. prednisolone 40 mg once daily for 10 days
NEMAGOUDA [38]	Quasi-RCT, NI, inpatient	125 (0)	63.3±10.2	74.4	AECOPD Excluded specific causes (e.g. heart failure), indication for MV or ICU	NI	NI/NI	Nebulised budesonide 8 mg·day^{-1} four times daily versus i.v. hydrocortisone 200 mg three times daily or p.o. prednisolone 40 mg·day^{-1} for 5 days
ODONCHIMEG [53]	RCT, NI, inpatient	120 (1.7)	59.2±7.3	71.7	Clinical AECOPD within 24 h in patients aged >40 years with SI ⩾10 pack-years and spirometric confirmation with FEV$_1$ <80% predicted Excluded heart failure	No	No/not high dose	Nebulised budesonide 2 mg·day^{-1} twice daily, inhaled budesonide 800–1200 μg·day^{-1} versus i.v. prednisolone 1 mg·kg^{-1}·day^{-1} twice daily for 10 days

TABLE 1 Continued								
First author [ref.], registry identifier	Study design	Participants n (withdrawn %)	Age years mean±SD	Male %	Inclusion diagnosis	Asthma	SCS/ICS (previous month)	Regimen
STÄLLBERG [54] NCT00259779/SPACE	RCT, DB, outpatient	113 (23.9)	66.9±9.5	51.4	Clinical AECOPD of moderate severity within 1 week in patients aged ⩾40 years with SI ⩾10 pack-years COPD for ⩾6 months (stage IIa or IIb, GOLD [55]) with FEV_1 30–60% predicted and S_{pO_2} ⩾92% after ambulatory treatment[¶¶] Excluded mild and severe AECOPD (respiratory failure, indication for hospital admission), AECOPD in the preceding month	No	Yes[¶¶]	Inhaled budesonide 1280 µg·day^{-1} four times daily *versus* p.o. prednisolone 30 mg once daily for 14 days
SUN [56]	RCT, NI, NI	30 (0)	62.4±7.6	56.7	AECOPD of bacterial infective aetiology in patients aged >50 years with SI ⩾20 pack-years and COPD per GOLD [49] Excluded severe heart, renal, hepatic and gastrointestinal disease, cancer, acute respiratory failure, acidosis, indication for ICU	No	No[¶]	Nebulised budesonide 6 mg·day^{-1} (twice daily) *versus* i.v. methylprednisolone 40 mg once daily for 3 days followed by p.o. 16 mg·day^{-1} twice daily (NI on total duration)
XIAO [57]	RCT, NI, inpatient	60 (0)	59±5.3	55	AECOPD Excluded heart disease, severe hepatic or renal dysfunction	NI	Not recently[¶]	Nebulised budesonide 3 mg·day^{-1} three times daily *versus* p.o. prednisone 0.5–1 mg·kg^{-1}·day^{-1} once daily and i.v. methylprednisolone 40 mg once daily for 5 days
YILMAZEL UCAR [58]	RCT, NI, inpatient	86 (10.5)	67.5±9.3	82.6	Clinical AECOPD as per GOLD [49] with indication for hospitalisation in patients aged >40 years with SI ⩾10 pack-years Excluded specific cause (*e.g.* heart failure), indication for ICU admission, systemic disease (*e.g.* diabetes mellitus, hypertension)	No	No/no[##] (recently)	Nebulised budesonide 4 mg·day^{-1} twice daily, 8 mg·day^{-1} twice daily *versus* i.v. methylprednisolone 40 mg once daily during hospitalisation (mean 9.3±4.5 days)
ZHANG [59]	RCT, NI, inpatient	98 (0)	65.3±NI	70.4	Clinical criteria for moderate to severe AECOPD as per the respiratory branch of the Chinese Medical Association guidelines [60] Excluded infection within 2 weeks, other chronic cardiopulmonary diseases, indication for MV	No	Not for 3 months/ NI	Nebulised budesonide 6 mg·day^{-1} three times daily *versus* p.o. prednisone 30 mg·day^{-1} once daily and i.v. methylprednisolone 80 mg once daily for 7 days

TABLE 1 Continued

First author [ref.], registry identifier	Study design	Participants n (withdrawn %)	Age years mean±SD	Male %	Inclusion diagnosis	Asthma	SCS/ICS (previous month)	Regimen
ZHAO [61]	RCT, NI, inpatient	150 (NI, probably 0)	62.9±NI	58.7	AECOPD as per the respiratory branch of the Chinese Medical Association guidelines [62], in patients aged >18 years Excluded systemic disease (history of diabetes, hypertension, severe autoimmunity, immunodeficiency, severe systemic infectious disease, heart, hepatic or renal insufficiency)	No	No[¶]	Nebulised budesonide 4 mg·day^{-1} twice daily *versus* p.o. prednisone 40 mg·day^{-1} for 7 days and i.v. methylprednisolone 1 mg·kg^{-1}·day^{-1} for 3 days followed by 0.5 mg·kg^{-1}·day^{-1} for 4 days
ZHENG [63]	RCT, DB, NI	107 (NI)	NI	NI	AECOPD	NI	NI/NI	Nebulised budesonide 8 mg·day^{-1} four times daily *versus* i.v. methylprednisolone 40 mg·day^{-1} for 7 days
ZHOU [64]	RCT, NI, NI	40 (0)	65.1±6.6	82.5	Clinical AECOPD as per GOLD diagnostic criteria [65] in patients with FEV$_1$ <1000 mL·min^{-1} Excluded indication for MV, heart failure, serious systemic disease AECOPD for 2.4±1.5 days prior to recruitment	No	No/NI	Nebulised budesonide 6 mg·day^{-1} three times daily *versus* p.o. prednisone 30 mg·day^{-1} three times daily for 7 days

SCS: systemic corticosteroids; ICS: inhaled corticosteroids; RCT: randomised controlled trial; DB: double-blinded; ED: emergency department; AECOPD: acute exacerbation of COPD; ATS: American Thoracic Society; ERS: European Respiratory Society; MV: mechanical ventilation; SB: single-blinded; NI: no information; ICU: intensive care unit; SI: smoking index; FEV$_1$: forced expiratory volume in 1 s; OL: open-label; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NYHA: New York Heart Association; FVC: forced vital capacity; S_{pO_2}: peripheral oxygen saturation. [#]: the whole study population with no specific data on the groups of interest; [¶]: not clarified whether systemic, inhaled or neither; [+]: the number of patients analysed in the groups of interest, with no information regarding randomised patients; [§]: participants were blinded ⩾10 out of 15 treatment days (during hospitalisation), but if discharged on days 11–15, they received OL SCS or ICS; [ƒ]: >1500 µg·day^{-1}; [##]: >1500 µg·day^{-1} of inhaled beclomethasone equivalent; [¶¶]: all participants received p.o. a single dose of prednisolone 30–50 mg or betamethasone 3–8 mg, along with ipratropium bromide and/or salbutamol (nebulised or inhaled *via* spacer), as ambulatory treatment for the exacerbation prior to randomisation/ICS were not permitted at study entry >1000 µg·day^{-1}.

Risk-of-bias assessment

All trials were deemed at a high risk of bias, mostly due to lack of blinding with potential bias in outcome measurement, unavailable data or per protocol analysis (figure 1).

Meta-analyses

Figure 2 and supplementary figure A2 feature the forest plots with the effect estimates for all meta-analyses. The GRADE evidence profile for the main clinically relevant outcomes is shown in table 2.

FIGURE 1 Risk-of-bias table.

a) Treatment failure during the intervention

First author [ref.]	Inhaled CS		Systemic CS		Weight	Risk ratio M-H, random (95% CI)
	Events	Total	Events	Total		
MAKAROVA [48]	3	37	1	41	14.1%	3.32 (0.36–30.58)
MALTAIS [50]	8	71	5	62	61.4%	1.40 (0.48–4.05)
NEMAGOUDA [38]	1	65	1	60	9.2%	0.92 (0.06–14.43)
ODONCHIMEG [53]	2	80	0	40	7.7%	2.53 (0.12–51.50)
STÄLLBERG [54]	2	58	0	55	7.7%	4.75 (0.23–96.69)
Total (95% CI)		311		258	100.0%	1.75 (0.76–4.02)
Total events	16		7			

Heterogeneity: Tau^2=0.00, Chi^2=1.20, df=4 (p=0.88); I^2=0%
Test for overall effect z=1.31 (p=0.19)

b) Breathlessness, mean change (pre-treatment to post-treatment)

First author [ref.]	Inhaled CS		Systemic CS		Weight	SMD IV, random (95% CI)
	Mean±SD	Total	Mean±SD	Total		
KAFEE [47]	2.37±0.54	45	2.49±0.6	45	37.6%	−0.21 (−0.62–-0.21)
STÄLLBERG [54]	0.28±0.2959	55	0.28±0.2565	54	45.7%	0.00 (−0.38–0.38)
ZHOU [64]	2.8±1.1	20	3±1.2	20	16.7%	−0.17 (−0.79–0.45)
Total (95% CI)		120		119	100.0%	−0.11 (−0.36–0.15)

Heterogeneity: Tau^2=0.00, Chi^2=0.58, df=2 (p=0.75); I^2=0%
Test for overall effect z=0.82 (p=0.41)
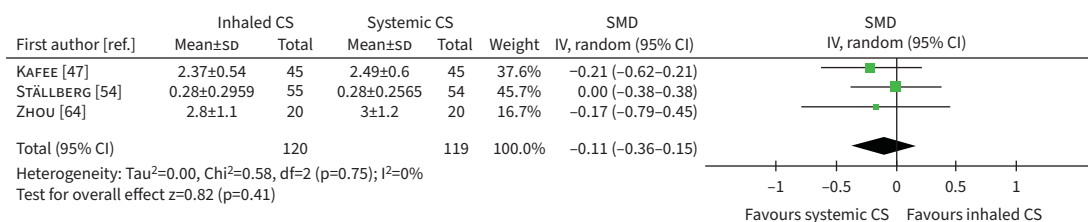
c) Breathlessness, post-treatment score

First author [ref.]	Inhaled CS		Systemic CS		Weight	SMD IV, random (95% CI)
	Mean±SD	Total	Mean±SD	Total		
KAFEE [47]	4.49±0.94	45	4.76±0.99	45	30.7%	−0.28 (−0.69–0.14)
MAKAROVA [48]	1.8±0.4	37	2±0.7	41	26.4%	−0.34 (−0.79–0.11)
NEMAGOUDA [38]	3±1	65	3±1	60	43.0%	0.00 (−0.35–0.35)
Total (95% CI)		147		146	100.0%	−0.18 (−0.41–0.05)

Heterogeneity: Tau^2=0.00, Chi^2=1.73, df=2 (p=0.42); I^2=0%
Test for overall effect z=1.50 (p=0.13)
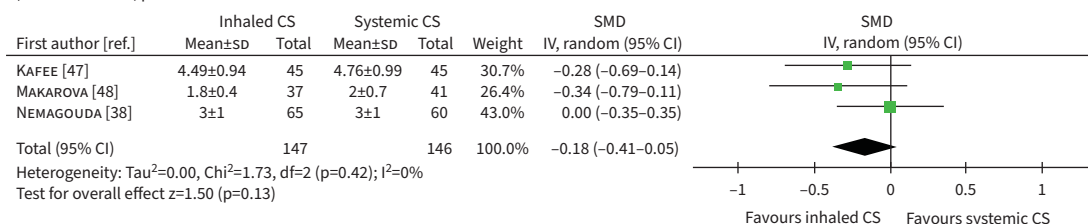
d) Serious adverse events during treatment

First author [ref.]	Inhaled CS		Systemic CS		Weight	Risk ratio M-H, random (95% CI)
	Events	Total	Events	Total		
MALTAIS [50]	8	71	5	62	83.2%	1.40 (0.48–4.05)
STÄLLBERG [54]	2	58	1	55	16.8%	1.90 (0.18–20.33)
Total (95% CI)		129		117	100.0%	1.47 (0.56–3.88)
Total events	10		6			

Heterogeneity: Tau^2=0.00, Chi^2=0.05, df=1 (p=0.82); I^2=0%
Test for overall effect z=0.78 (p=0.44)
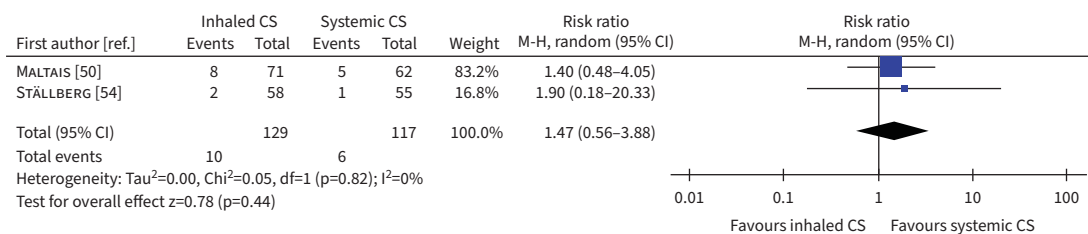
e) Any adverse event during treatment

First author [ref.]	Inhaled CS		Systemic CS		Weight	Risk ratio M-H, random (95% CI)
	Events	Total	Events	Total		
GONG [43]	8	26	12	27	9.9%	0.69 (0.34–1.41)
MALTAIS [50]	38	71	43	62	68.0%	0.77 (0.59–1.01)
MIRICI [51]	1	22	1	22	0.7%	1.00 (0.07–15.00)
STÄLLBERG [54]	15	58	14	55	12.8%	1.02 (0.54–1.90)
SUN [56]	4	15	6	15	4.6%	0.67 (0.23–1.89)
ZHENG [63]	6	53	5	54	4.0%	1.22 (0.40–3.76)
Total (95% CI)		245		235	100.0%	0.80 (0.64–1.00)
Total events	72		81			

Heterogeneity: Tau^2=0.00, Chi^2=1.53, df=5 (p=0.91); I^2=0%
Test for overall effect z=1.93 (p=0.05)

f) Health-related quality of life, post-treatment score

First author [ref.]	Inhaled CS		Systemic CS		Weight	SMD IV, random (95% CI)
	Mean±SD	Total	Mean±SD	Total		
DING [41]	21.73±9.98	191	21.46±6.6	179	33.6%	0.03 (−0.17–0.24)
MAKAROVA [48]	17.2±4	37	16.8±3.4	41	11.0%	0.11 (−0.34–0.55)
NEMAGOUDA [38]	68.95±6.75	65	70.8±7.09	60	16.1%	−0.27 (−0.62–0.09]
ODONCHIMEG [53]	35.94±11.44	78	33.4±11.3	40	14.2%	0.22 (−0.16–0.60]
STÄLLBERG [54]	2.52±1.19	45	2.32±1.11	51	13.1%	0.17 (−0.23–0.57]
ZHANG [59]	4.63±0.65	33	4.82±0.62	65	12.1%	−0.30 (−0.72–0.12]
Total (95% CI)		449		436	100.0%	−0.00 (−0.16–0.16)

Heterogeneity: Tau^2=0.01, Chi^2=6.44, df=5 (p=0.27); I^2=22%
Test for overall effect z=0.03 (p=0.97)

Primary outcomes

Treatment success, defined as a dichotomous measure of the overall outcome of the exacerbation, was not assessed in any trial. Treatment failure, defined as lack of efficacy, deterioration or need for treatment intensification, had a similar occurrence between groups during treatment, as shown in five trials with 569 participants (relative risk 1.75, 95% CI 0.76–4.02, I^2=0%, low certainty) [38, 48, 50, 53, 54].

Breathlessness was evaluated in eight trials with 721 participants, where inhaled corticosteroids showed similar impact to systemic corticosteroids. Specifically, change from pre-treatment values was captured in the Borg, modified Borg or a nonvalidated scale in three trials [47, 54, 64]. Treatment effects were similar between groups (standardised mean difference, SMD −0.11, 95% CI −0.36–0.15, I^2=0%, 239 participants, low certainty). The post-treatment scores on the modified Medical Research Council and modified Borg scales did not differ significantly between groups, according to three trials, including one of the above [38, 47, 48] (SMD −0.18, 95% CI −0.41–0.05, I^2=0%, 293 participants, low certainty). Finally, two further trials (146 participants) reported similar impact across treatment groups, but did not provide specific numerical data to pool [42, 58].

Serious adverse events were monitored in two trials during treatment, showing a similar rate in both arms (relative risk 1.47, 95% CI 0.56–3.88, I^2=0%, 246 participants, low certainty) [50, 66]. Longer follow-up was assessed in one trial that did not reveal between-group differences (3 months follow-up, relative risk 0.63, 95% CI 0.24–1.66, 113 participants) [66].

Secondary outcomes

Health-related quality of life showed similar improvement with both inhaled and systemic corticosteroids across six trials with 885 participants. These used the St George's Respiratory Questionnaire (SGRQ) [38], SGRQ-C [53], the COPD Assessment Test [41, 48], the clinical COPD questionnaire (CCQ) [54] and modified Guyatt measure [59] to capture post-treatment scores. When pooling data with the SMD, we noted a balanced effect in both groups (SMD 0.0, 95% CI −0.16–0.16, I^2=22%, moderate certainty). The number of patients with improvement in SGRQ did not appear to differ between groups, as shown in one of the aforementioned studies (relative risk 1.07, 95% CI 0.93–1.23, 125 participants, very low certainty) [38].

The overall symptom score, comprising breathlessness, cough and wheezing, with or without sputum, was similar in both groups post-treatment (SMD 0.00, 95% CI −0.91–0.90, I^2=90%, 200 participants, very low certainty), according to two trials using a nonvalidated score [37] or the symptoms subscore of the SGRQ-C [53]. Improvement in post-treatment scores was reportedly similar in the STÄLLBERG et al. [54] (109 participants, CCQ symptoms subscore) and DJORDJEVIC et al. [42] (60 participants, score not described) trials. Cough [48, 54] and sputum [48] were scarcely reported, without any significant between-group difference.

The length of hospital stay was assessed in seven trials with 1069 participants. We found similar hospitalisation duration in both treatment groups (MD −0.59, 95% CI −1.88–0.70, I^2=89%, three trials with 613 participants, low certainty) [38, 41, 48]. Three other trials reported narratively consistent results (326 participants) [50, 58, 63]. The median hospital stay ranged from 7 to 11.3 days and from 6 to 13 days among patients receiving inhaled and systemic corticosteroids, respectively [38, 41, 48, 50]. Prolonged hospitalisation, reaching 10 days [50] or more [38, 45], was proportionate in both groups (relative risk 1.03, 95% CI 0.73–1.45, I^2=27%, three trials with 340 participants, low certainty). The number of patients who were discharged by day 5 from recruitment, was documented in one study [38], with a tendency to favour inhaled over systemic corticosteroids (relative risk 1.78, 95% CI 1.00–3.14, 125 participants, very low certainty).

Among patients recruited at a primary health centre or the emergency department, hospital admission was more frequent in systemic corticosteroid group (relative risk 0.70, 95% CI 0.53–0.93, I^2=0%, two trials with 160 participants, low certainty) [39, 54]. Among hospitalised patients, indication for mechanical ventilation or admission to the ICU did not differ between groups (relative risk 0.82, 0.17–3.89, I^2=0%, four trials, 388 participants, low certainty) [38, 50, 51, 58].

TABLE 2 Evidence profile according to Grading of Recommendations Assessment, Development and Evaluation methodology for clinical outcomes up to treatment completion and at longest follow-up

	Certainty assessment						Summary of findings				
	Trials (participants) n (N)	Risk of bias	Inconsistency	Imprecision	Indirectness	Other	Overall certainty	Noninferiority	ICS	SCS	Anticipated absolute	Relative (95% CI)
Treatment failure	5 (569)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Low	ICS noninferiority	16/311 (5.1)	7/258 (2.7)	20 more per 1000 (7 fewer to 82 more)	Relative risk 1.75 (0.76–4.02)
Breathlessness								ICS noninferiority				
Mean change	3 (239)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Low		120	119	0.11 lower (0.36 lower to 0.15 higher)	SMD −0.11 (−0.36–0.15)
Score	3 (293)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Low		147	146	0.18 lower (0.41 lower to 0.05 higher)	SMD −0.18 (−0.41–0.05)
Serious adverse events								ICS noninferiority				
Overall	2 (246)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Low		10/129 (7.8)	6/117 (5.1)	24 more per 1000 (23 fewer to 148 more)	Relative risk 1.47 (0.56–3.88)
Up to 3 months	1 (113)	Serious[#]	Not applicable	Very serious[¶]	Not serious	Not serious	Very low		6/58 (10.3)	9/55 (16.4)	61 fewer per 1000 (124 fewer to 108 more)	Relative risk 0.63 (0.24–1.66)
Health-related quality of life								ICS noninferiority				
Score	6 (885)	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate		449	436	0.0 higher (0.16 lower to 0.16 higher)	SMD 0.0 (−0.16–0.16)
Improved	1 (125)	Serious[#]	Not applicable	Very serious[¶]	Not serious	Not serious	Very low		58/65 (89.2)	50/60 (83.3)	58 more per 1000 (58 fewer to 192 more)	Relative risk 1.07 (0.93–1.23)
Length of hospital stay								ICS noninferiority				
Overall	Serious[#]	Serious[+]	Not serious	Not serious	Not serious	Serious[#]	Low		322	291	0.59 lower (1.88 lower to 0.7 higher)	MD −0.59 (−1.88–0.7)
Prolonged (≥10 days)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Serious[#]	Low		60/178 (33.7)	54/162 (33.3)	10 more per 1000 (90 fewer to 150 more)	Relative risk 1.03 (0.73–1.45)
Shorter (5 days)	Serious[#]	Not applicable	Very serious[¶]	Not serious	Not serious	Serious[#]	Very low		25/65 (38.5)	13/60 (21.7)	169 more per 1000 (0 fewer to 464 more)	Relative risk 1.78 (1.00–3.14)

TABLE 2 Continued

	Trials (participants) n (N)	Certainty assessment						Summary of findings				
		Risk of bias	Inconsistency	Imprecision	Indirectness	Other	Overall certainty	Noninferiority	ICS	SCS	Anticipated absolute	Relative (95% CI)
Indication for higher level of care												
Hospital	2 (160)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low	ICS superiority	19/82 (23.2)	23/78 (29.5)	**88 fewer per 1000 (139 fewer to 21 fewer)**	**Relative risk 0.70 (0.53–0.93)**
MV-ICU	4 (388)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low	ICS noninferiority	3/211 (1.4)	3/177 (1.7)	3 fewer per 1000 (14 fewer to 49 more)	Relative risk 0.82 (0.17–3.89)
Future exacerbations								ICS noninferiority				
3 months	1 (109)	Serious#	Not applicable	Very serious¶	Not serious	Not serious	Very low		11/55 (20.0)	10/54 (18.5)	15 more per 1000 (93 fewer to 246 more)	Relative risk 1.08 (0.50–2.33)
Relative event rate (1–3 months)	2 (184)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low		23/93 (24.7)	22/91 (24.2)	5 more per 1000 (92 fewer to 169 more)	1.02 (0.62–1.70)
Rate (12 months)	1 (126)	Serious#	Not applicable	Very serious¶	Not serious	Not serious	Very low		71	55	0.08 lower (0.31 lower to 0.15 higher)	MD −0.08 (−0.31–0.15)
Time-to-next	1 (126)	Serious#	Not applicable	Very serious¶	Not serious	Not serious	Very low		71	55	0.46 higher (0.75 lower to 1.67 higher)	MD 0.46 (−0.75–1.67)
Severe	2 (203)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low		4/102 (3.9)	5/101 (5.0)	**2 more per 1000 (46 fewer to 664 more)**	**Relative risk 1.05 (0.08–14.42)**
Severe: relative event rate	2 (184)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low		6/93 (6.5)	7/91 (7.7)	**9 fewer per 1000 (55 fewer to 130 more)**	**0.88 (0.29–2.69)**
Mortality								ICS noninferiority				
Up to day 10	3 (328)	Serious#	Not applicable	Serious¶	Not serious	Not serious	Low		0/171 (0.0)	1/157 (0.6)	**5 fewer per 1000 (6 fewer to 38 more)**	**Relative risk 0.29 (0.01–7.03)**
Up to 3 months	2 (188)	Serious#	Not serious	Serious¶	Not serious	Not serious	Low		0/96 (0.0)	2/92 (2.2)	15 fewer per 1000 (21 fewer to 44 more)	Relative risk 0.32 (0.03–3.03)

Continued

TABLE 2 Continued

		Certainty assessment						Summary of findings				
	Trials (participants) n (N)	Risk of bias	Inconsistency	Imprecision	Indirectness	Other	Overall certainty	Noninferiority	ICS	SCS	Anticipated absolute	Relative (95% CI)
Adverse events								ICS noninferiority				
Overall	6 (480)	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate		72/245 (29.4)	81/235 (34.5)	69 fewer per 1000 (124 fewer to 0 fewer)	Relative risk 0.80 (0.64–1.0)
Up to 3 months	1 (113)	Serious[#]	Not applicable	Very serious[¶]	Not serious	Not serious	Very low		18/58 (31.0)	15/55 (27.3)	38 more per 1000 (98 fewer to 281 more)	Relative risk 1.14 (0.64–2.03)
Hyperglycaemia during treatment	9 (1114)	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate	ICS superiority	17/535 (3.2)	78/579 (13.5)	**97 fewer per 1000 (116 fewer to 63 fewer)**	**Relative risk 0.28 (0.14–0.53)**
Fungal infection during treatment												
Oral	4 (431)	Serious[#]	Not serious	Serious[¶]	Not serious	Not serious	Low	SCS superiority	14/202 (6.9)	0/229 (0.0)	**No oral fungal infections observed with SCS**	**Relative risk 7.90 (1.82–34.30)**
Any	1 (410)	Serious[#]	Not applicable	Serious[¶]	Not serious	Not serious	Low	ICS noninferiority	5/220 (2.3)	11/190 (5.8)	35 fewer per 1000 (50 fewer to 6 more)	Relative risk 0.39 (0.14–1.11)

Data are presented as n or n/N (%), unless otherwise stated. Bold type represents significant between-group difference. ICS: inhaled corticosteroids; SCS: systemic corticosteroids; MV: mechanical ventilation; ICU: intensive care unit; SMD: standardised mean difference; MD: mean difference. [#]: all randomised controlled trials were deemed at a high risk of methodological bias; [¶]: broad confidence intervals and/or insufficient overall study population; [+]: no overlap in confidence intervals.

The risk of future exacerbations was assessed in five trials with 513 participants and was similar between groups. The number of patients experiencing an exacerbation within 3 months did not differ between groups (relative risk 1.08, 95% CI 0.50–2.33, one trial with 109 participants, very low certainty) [54]. Two trials with 184 participants recorded a similar number of total exacerbations between groups during follow-up for 1 month [45] or 3 months [54] after discharge (relative event rate 1.02, 95% CI 0.62–1.70, I^2=0%, low certainty). Another trial followed-up 126 patients for 12 months [41], demonstrating a similar rate (MD −0.08, 95% CI −0.31–0.15, very low certainty) and mean time to next exacerbation in months (MD 0.46, 95% CI −0.75–1.67, very low certainty) in both treatment groups. Mean time to next exacerbation up to 3 months was also similar between groups according to another trial with no numerical data to pool [54]. The risk for severe exacerbations leading to hospital admission did not differ between groups either (relative risk 1.05, 95% CI 0.08–14.42, I^2=60%, two trials with 203 participants, low certainty; relative event rate 0.88, 95% CI 0.29–2.69, I^2=3%, two trials with 184 participants, low certainty) [38, 45, 48, 54].

Mortality did not differ between groups at up to 10 days of treatment (relative risk 0.29, 95% CI 0.01–7.03, three trials with 328 participants) [45, 50, 66] and up to 3 months follow-up (relative risk 0.32, 95% CI 0.03–3.03, I^2=0%, two trials with 188 participants, low certainty) [45, 66].

Adverse events tended to be more frequent among patients receiving systemic *versus* inhaled corticosteroids (relative risk 0.80, 95% CI 0.64–1.0, I^2=0%, six trials with 480 participants, moderate certainty [43, 50, 51, 56, 63, 66]. Another trial reported narratively similar occurrence between treatment groups [58]. The risk for adverse events at longest follow-up (3 months) was similar in both groups (relative risk 1.14, 95% CI 0.64–2.03, 113 participants) [66]. Hyperglycaemia affected more patients during treatment with systemic than inhaled corticosteroids (relative risk 0.28, 95% CI 0.14–0.53, I^2=15%, nine trials with 1114 participants, moderate certainty) [41, 50, 56–59, 61, 63, 64]. This was corroborated by a further trial [48] recording a 2.9-fold higher rate (p=0.026) in patients treated with systemic *versus* inhaled corticosteroids (78 participants). Oral fungal infection was more frequent in the inhaled treatment group (relative risk 7.90, 95% CI 1.82–34.30, I^2=0%, four trials with 431 participants, low certainty) [37, 58, 61, 66]. Conversely, the rate of any fungal infection (local or systemic) did not differ between groups (relative risk 0.39, 95% CI 0.14–1.11, one trial with 410 participants, low certainty) [41].

The partial pressure of oxygen in arterial blood (P_{aO_2}, in mmHg) showed similar mean change from pre-treatment with both corticosteroid routes (MD −4.33, 95% CI −10.36–1.69, I^2=67%, two trials with 283 participants [41, 64]; narrative in another trial with 82 participants [45]). There was a tendency for higher post-treatment values with systemic corticosteroids, which were not clinically important (MD −1.33, 95% CI −2.64–−0.02, I^2=34%, six trials with 695 participants) [37, 41, 45, 59, 61, 64]. Notably, P_{aO_2} measurements were not performed explicitly under room air conditions in all participants [37, 41, 50, 59, 61], thus rendering results uninformative. When excluding these trials in a sensitivity *ad hoc* analysis, we found no between-group difference (post treatment values MD −1.25, 95% CI −3.34–0.84, I^2=0%, two trials with 122 participants) [45, 64]. Three other trials with 156 participants [51, 56, 58] reported nonsignificant between-group differences, with no numerical data to be included in the meta-analysis. The partial pressure of carbon dioxide in the arterial blood (in mmHg) mean change from pre-treatment was similar between groups (MD 0.60, 95% CI −1.84–3.03, I^2=47%, two trials with 283 participants) [41, 64]. However, one trial that was not pooled reported a mean change that exceeded 3.9 mmHg, favouring systemic over inhaled corticosteroids (82 participants); however, this difference is not clinically significant [45]. Post-treatment values did not differ significantly across six trials with 695 participants (MD −0.03, −1.01–0.94, I^2=34%) [37, 41, 45, 59, 61, 64]. Two further studies that were not pooled [51, 56] did not find any between-group difference either (70 participants). Both inhaled and systemic corticosteroids showed similar impact on oxygen saturation post-treatment values across six trials (535 participants) [38, 39, 45, 48, 51, 58] using either pulse oximetry or arterial blood measurements (MD 0.28, −0.28–0.85, I^2=54%, four trials with 369 participants) [38, 39, 45, 48].

Disease progression was not assessed in line with the ERS COPD exacerbations core outcome set [31] in any trial. One trial with 98 participants [50] reported on FEV_1 mean change from baseline disease state, with similar results between groups on the third treatment day. Mean change from pre-treatment generally did not differ between groups (mean change in percentage predicted values: MD 0.10, 95% CI −3.13–3.33, one trial with 109 participants that assessed FEV_1 % before and after treatment [66]; mean change MD 0.03 L, 95% CI −0.05–0.11 L, I^2=73%, three trials with 188 participants [41, 47, 64]; narrative in two trials with 200 participants [45, 53]). Post-treatment FEV_1 values were similar in both groups (MD 0.18% pred, 95% CI −2.69–3.04% pred, I^2=85%, eight trials with 804 participants) [38, 43, 45, 48, 53, 54, 59, 61], but there was a tendency in favour of systemic corticosteroids for measurements in litres (MD −0.05 L,

95% CI −0.12–0.03 L, I^2=68%, seven trials with 703 participants) [37, 38, 41, 47, 54, 57, 61]. Two additional trials that we could not include in our meta-analysis, due to insufficient numerical data, did not yield between-group differences [56, 58]. Evaluation of FVC yielded similar results across the treatment groups [38, 45, 48, 53, 57, 58].

Treatment adherence was quantified in one trial documenting an average compliance that reached 89.9% and 96.7% in the inhaled and systemic corticosteroid groups, respectively [54].

Worsening of symptoms after initial treatment, activities of daily living, development of pneumonia or resistant bacteria were not evaluated in any trial.

Secondary time points analysis
Apart from our main analysis at post-treatment time points, we assessed all outcomes up to 7 days and beyond 7 days. These analyses yielded consistent results and are available in the supplementary material.

Subgroups and sensitivity analyses
The supplementary material features all sensitivity and subgroups analyses, which were generally consistent with our main analysis. No subgroup differences emerged, but these analyses were informed by small overall study populations.

Discussion
Summary of findings
This systematic review and meta-analysis, based on 20 randomised and quasirandomised trials totalling 2140 participants with COPD exacerbations, did not reveal evidence of superiority of systemic over inhaled corticosteroids in any of the clinically important efficacy outcomes (low certainty). We found similar rates of serious adverse events between groups (low certainty), while inhaled corticosteroids tended to reduce the risk of any adverse event and of hyperglycaemia (moderate certainty). Low-certainty evidence suggested an increased risk of oral fungal infection with inhaled corticosteroids, while the risk of any fungal infection was similar in both groups. Appropriately designed and powered RCTs are needed to confirm these findings.

Overall completeness and applicability of evidence
There was significant heterogeneity in corticosteroid regimens across the included RCTs. Although a dose of oral prednisone 40 mg·day^{-1} for 5 days is recommended as sufficient [26, 67], the controls received variable systemic corticosteroids regimens at nonequivalent dosages, which may have introduced some heterogeneity in our findings, but were generally accepted in clinical practice at the time these trials were conducted. All RCTs used high doses of inhaled budesonide, ranging between 1.5–8 mg·day^{-1} *via* nebulisers (median dose of 8 mg·day^{-1}) and 800–1280 µg·day^{-1} *via* inhaler devices. Different administration regimens of nebulised budesonide have been evaluated for COPD exacerbations in head-to-head comparisons [53, 58, 68], but the evidence remains inconclusive. We performed subgroup analyses based on budesonide doses, although the limited number of available studies, variable treatment duration across the trials, and heterogeneity in the control groups weakened comparability. These did not reveal significant differences.

Two RCTs evaluating asthma demonstrated that patients quadrupling their inhaled corticosteroid dose to an average 2000 µg·day^{-1} or 3200 µg·day^{-1} beclomethasone equivalent may be less likely to require oral corticosteroids during exacerbations [69, 70]. Most trials in this meta-analysis for COPD exacerbations did not document the maintenance inhaled corticosteroids daily dose delivered during stable disease state to allow for an estimation of relative increase during exacerbations.

Duration of exacerbation symptoms prior to recruitment was generally not documented, with three trials recording a mean 2.4–11 days [47, 50, 64]. Considering the significance of timely treatment initiation to ensure therapeutic benefit [71, 72], we note that our findings may have been weakened by potential delay in corticosteroids administration. Exacerbation treatment with corticosteroids prior to patient enrolment was also unclear in some RCTs, while in one trial [54], all participants received oral corticosteroid as ambulatory treatment prior to randomisation, potentially impacting the outcomes. However, we did not note any difference when excluding these RCTs in a sensitivity analysis. Additionally, concomitant treatments, such as antibiotics, bronchodilators and mucolytics may have impacted the outcomes, and potential imbalances between treatment groups were not reported in all RCTs [73, 74].

Many RCTs excluded participants with common comorbidities, including heart failure, diabetes mellitus, and hypertension [22, 75–78], thus limiting the generalisability of our findings in real-life COPD patients. These may decompensate due to systemic corticosteroids effects, which include hyperglycaemia, fluid retention, elevated blood pressure, myopathy, weight gain, increased bone fracture risk, susceptibility to infections, psychological disorders, and adrenal suppression [12–18]. Decompensation of comorbidities could further aggravate COPD exacerbations [9], as well as the overall patients' status, and affect disease prognosis [79, 80]. On the other hand, it is postulated that systemic inflammation induced during an exacerbation (spill-over effect) may be associated with systemic complications and decompensation of comorbidities, such as myocardial infarction or stroke [81–84]. While inhaled administration of corticosteroids may be associated with reduced treatment burden, it might not adequately address systemic inflammation spill-over. Therefore, future trials should be adequately powered to assess whether inhaled corticosteroids are optimal for patients with comorbidities.

Most included studies also lacked data on exacerbation rate and repeated corticosteroid use. Cohort studies have revealed that 15.5% [85] to 22.4% [86] of COPD patients experienced frequent exacerbations (two or more annually), while ~33% of patients with severe exacerbations required subsequent hospitalisations (at least two) [87]. Frequent exacerbators have an estimated mean 2.89 exacerbations per year [88–90] that tend to cluster together in time [91] and suffer from a higher disease burden [92]. These patients, exposed to a higher cumulative corticosteroid dose, are more susceptible to side-effects [23, 24] and might benefit more from systemic corticosteroids avoidance during exacerbations, but we could not assess this in the absence of adequate data.

Emerging evidence suggests that only 20–40% of all exacerbations, which are characterised by enhanced airway eosinophilia, respond to corticosteroids [4, 93]. High sputum and blood eosinophil count serve as surrogate markers of airway eosinophilic inflammation and of treatment response to corticosteroids, both during stable COPD and exacerbations [94–96]. Unfortunately, none of the included studies recruited exclusively patients more likely to respond to corticosteroids. Potential lack of clinical response to steroids by a significant proportion of patients (and trial participants) may dilute and conceal potential differences in treatment effects. Future trials are warranted to assess inhaled corticosteroids efficacy and safety as a targeted therapeutic intervention for eosinophilic exacerbations only.

Comparison to previous evidence syntheses and guidelines

Our findings are consistent with previous meta-analyses comparing inhaled to systemic corticosteroids [97–101]. However, our rigorous systematic searches revealed additional eligible RCTs, and a larger overall study population. As a result, some of our analyses were informed by a broader evidence base, while we were also able to address additional, clinically relevant outcomes. Indeed, we assessed all clinically important outcomes that have been prioritised in the ERS COPD Exacerbation core outcome set [31] and are considered more critical for decision making by patients, health professionals, and other relevant stakeholder groups [102]. Overall, this meta-analysis represents the most apposite currently available evidence and highlights important evidence gaps.

Current guidelines recommend cautious administration of systemic corticosteroids for COPD exacerbations [9], highlighting the considerable risk of adverse events [11], pneumonia, sepsis and death [19]. Based on four RCTs, GOLD views nebulised budesonide as a potential alternative to intravenous methylprednisolone for COPD exacerbations [9].

Strengths and limitations

We adhered to Cochrane and GRADE methodology for appraising all relevant RCTs, performing meta-analysis and rating the certainty of evidence. However, the certainty of evidence was low to very low for most outcomes according to GRADE. There are several limitations in the design of the included trials and all were deemed at high risk of bias. Many trials did not assess clinically pertinent outcomes or did not provide adequate data to pool, thus limiting potential for powered meta-analyses. We reported both quantitatively but also narratively presented findings to minimise potential bias in our meta-analysis. Future trials should adopt the ERS COPD Exacerbations core outcome set [31] to facilitate comparability and report on the outcomes that matter most to patients and clinicians.

Six trials did not explicitly exclude patients with concomitant asthma, but we did not observe any impact on our findings when excluding them in a sensitivity analysis. Smoking history, age and spirometry criteria to establish a reliable COPD diagnosis were also not thoroughly documented in most trials. We performed rigorous sensitivity analyses, but did not find sufficient data for our pre-specified subgroups analyses. Unfortunately, we had no access to three potentially eligible studies [103–105].

Conclusion

This systematic review that accumulates currently available evidence, supports with low certainty that high-dose inhaled corticosteroids may not be inferior to systemic corticosteroid administration for unselected patients with moderate or severe COPD exacerbations. Appropriately designed and powered RCTs are warranted to confirm these findings.

Questions for future research

Rigorous RCTs assessing precision-medicine approaches are needed to further compare the safety and efficacy of inhaled *versus* systemic corticosteroids for COPD exacerbations with enhanced airway eosinophilia. In addition, the comparative safety and effectiveness of these interventions should be evaluated in patients experiencing frequent exacerbations and real-life patients, including those with significant cardiovascular and other comorbidities. The adoption of all clinically important outcomes prioritised in the ERS COPD exacerbations core outcome set will increase their clinical value and potentiate comparability across RCTs.

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