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Blood Eosinophils as a Modifier of Inhaled Corticosteroid Treatment Effects in Adults With Non-Cystic Fibrosis Bronchiectasis: A Systematic Review

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Abstract

Inhaled corticosteroids (ICS) are widely prescribed in non-cystic fibrosis bronchiectasis despite guideline recommendations that restrict their use to patients with asthma, chronic obstructive pulmonary disease (COPD), or allergic bronchopulmonary aspergillosis. This systematic review evaluated whether the evidence supports the blood eosinophil count (BEC) as a modifier of ICS effects in adults with bronchiectasis. Following PRISMA 2020, PubMed/MEDLINE was searched to November 4, 2026, supplemented by Google Scholar and citation searching. Peer-reviewed original studies reporting ICS effects by BEC stratum were eligible. Risk of bias was assessed with the Newcastle-Ottawa Scale, and findings were synthesized narratively, with approximate tests of interaction where stratum-specific estimates allowed.

Seven observational studies (2023-2026) from six health systems were included; no eligible randomized trial was identified. In all five studies assessing exacerbations, ICS use was associated with fewer exacerbations in the high-BEC stratum but not in lower strata, although no study formally tested the difference between strata (for example, adjusted hazard ratio 0.137; 95% CI 0.034-0.553 for triple therapy at BEC ≥300 cells/μL). In COPD-bronchiectasis overlap, ICS-associated pneumonia was observed at BEC ≤300 cells/μL (adjusted odds ratio 1.56) but not above it (0.89); the reported interaction was significant, but our recalculation was inconclusive (P = 0.03-0.09) because of an internally inconsistent published confidence interval. ICS was also associated with a higher risk of first *Pseudomonas aeruginosa* isolation at intermediate and high BEC. Four studies were of good quality and three of moderate quality.

Eosinophil-stratified estimates pointed in a similar direction, but differences between strata were rarely tested and, when tested, were borderline or uncertain. BEC is therefore a hypothesis-generating, not validated, biomarker for ICS selection, and the evidence does not support any BEC threshold for starting or withdrawing ICS. Biomarker-stratified randomized trials using repeated BEC measurements are required before BEC-guided ICS prescribing can be recommended.

Categories: Pulmonology
Keywords: blood eosinophil count, bronchiectasis, eosinophilic bronchiectasis, exacerbations, inhaled corticosteroids, pseudomonas aeruginosa, systematic review, treatable traits

Introduction And Background

Non-cystic fibrosis bronchiectasis is a chronic airway disease characterized by permanent bronchial dilatation, impaired mucociliary clearance, recurrent infection, and persistent inflammation that drives exacerbations, loss of lung function, and poor quality of life. These components interact in a self-perpetuating cycle in which impaired mucus clearance permits chronic bacterial infection, which sustains predominantly neutrophilic airway inflammation, protease release, and further structural damage [1]. The recorded burden of the disease is increasing; in the United Kingdom, prevalence rose substantially between 2004 and 2013, reaching approximately 566 per 100,000 women and 486 per 100,000 men [2]. Exacerbations are the dominant clinical events; exacerbation frequency behaves as a stable phenotypic trait, and patients with three or more exacerbations per year have more hospital admissions, poorer quality of life, and higher mortality [3]. International guidance does not support the routine use of inhaled corticosteroids (ICS) in adults with bronchiectasis and recommends their use mainly when asthma, chronic obstructive pulmonary disease (COPD), or allergic bronchopulmonary aspergillosis coexist [4]. This position reflects the results of randomized controlled trials summarized in a Cochrane review, which found insufficient evidence that ICS

improve lung function, exacerbation frequency, or quality of life in unselected adults with stable bronchiectasis [5]. Despite this, ICS remain among the most frequently prescribed maintenance therapies in bronchiectasis registries, frequently without a guideline-concordant indication, and their immunosuppressive properties raise concern in a disease dominated by chronic bacterial infection [6].

Bronchiectasis has traditionally been viewed as a neutrophilic disease, but a clinically relevant eosinophilic subset has now been characterized. In a European multicohort study, approximately 20% of patients without asthma had blood eosinophil counts (BEC) of ⩾300 cells/μL, and, after accounting for infection, elevated eosinophil counts were associated with a shorter time to the next exacerbation [7]. Clustering analyses of the Spanish bronchiectasis registry also showed that BEC separates patients into phenotypes with different severity, systemic inflammation, and clinical outcomes [8]. In COPD, BEC is an established predictor of ICS benefit, and low eosinophil counts combined with chronic bronchial infection identify patients in whom ICS increase pneumonia risk [9]. Together, these observations suggest that BEC might also identify the subgroup of bronchiectasis patients who could benefit from ICS and those in whom ICS may be harmful.

Two distinctions are central to this question. First, a prognostic biomarker identifies patients at higher risk of an outcome irrespective of treatment, whereas a predictive biomarker, or treatment-effect modifier, identifies patients in whom the effect of a specific treatment differs; demonstrating the latter requires a direct comparison of treatment effects across biomarker strata, preferably by a formal treatment-by-biomarker interaction test [10]. The observation that eosinophilia predicts exacerbations therefore does not, by itself, show that it predicts ICS response. Second, the rationale for ICS differs between bronchiectasis without other airway disease and bronchiectasis coexisting with asthma or COPD, in which ICS already have an established role in selected patients [4,9], so evidence from these populations should be interpreted separately.

Early hypothesis-generating support came from post hoc analyses of earlier randomized trials, in which inhaled fluticasone improved quality of life in patients with higher blood eosinophil levels [11] and pooled trial data suggested fewer exacerbations among patients with blood eosinophilia who received ICS [12]. However, these analyses were small and not uniformly concordant: a similar analysis of an inhaled budesonide trial found that blood eosinophils did not predict treatment response [13]. Commentators have since argued that ICS prescribing in bronchiectasis and COPD should be guided by biomarkers rather than by diagnostic labels [14]. However, the subsequent observational literature has used different eosinophil thresholds, populations, comparators, and outcomes, and some studies have reported infection-related harms. This systematic review therefore aimed to identify and critically appraise peer-reviewed original studies in adults with non-cystic fibrosis bronchiectasis in order to determine whether the available evidence supports BEC as a modifier of both the benefits and the risks of ICS, rather than presuming that such effect modification exists.

Review

Methods

Protocol and Reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [15], and the narrative synthesis was reported with reference to the Synthesis Without Meta-analysis (SWiM) guideline [16]. The review protocol was defined a priori but was not prospectively registered. The protocol is available from the corresponding author on request; its key elements, and all changes made after the protocol was finalized, including those introduced during peer review, are listed in Appendix A. Ethical approval was not required because only published data were analyzed.

Eligibility Criteria

Eligibility criteria were defined using the PICOS framework (Table *1*). Studies were eligible if they enrolled adults (⩾18 years) with non-cystic fibrosis bronchiectasis confirmed by computed tomography or a physician diagnosis, including bronchiectasis coexisting with COPD; evaluated maintenance ICS, alone or in combination with long-acting bronchodilators; compared ICS users with non-users or with ICS-free inhaled regimens; and reported a clinical outcome within at least two BEC strata, a BEC-by-ICS interaction, or a BEC threshold predicting ICS response. Only peer-reviewed original research articles were included. Narrative and systematic reviews, meta-analyses, editorials, letters and research letters, conference abstracts, case reports, study protocols, and preprints were excluded, as were studies of cystic fibrosis, pediatric populations, asthma without bronchiectasis, systemic corticosteroids, or biologic therapies. As prespecified, a publication-date restriction was to be applied only if 10 or more studies met all other criteria; because fewer than 10 did, no date restriction was applied.

PICOS element	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years) with non–cystic fibrosis bronchiectasis (CT-confirmed or physician-diagnosed), including bronchiectasis–COPD overlap	Cystic fibrosis; pediatric populations; asthma or COPD without bronchiectasis
Intervention/exposure	Maintenance ICS (monotherapy or with LABA ± LAMA) with a measured blood eosinophil count	Systemic corticosteroids; biologic therapies
Comparator	No ICS, matched non-users, or ICS-free inhaled therapy, with effects compared across BEC strata	No comparator; no BEC stratification or interaction analysis
Outcomes	Exacerbations, hospitalization, lung function, pneumonia, airway infection, mortality, or quality of life reported by BEC stratum, as a BEC × ICS interaction, or as a BEC cut-off for ICS response	Outcomes not reported by BEC
Study design	Peer-reviewed original research: randomized trials or post hoc trial analyses, cohort, and case-control studies	Reviews, meta-analyses, editorials, letters, conference abstracts, case reports, protocols, preprints

TABLE 1: Eligibility criteria according to the PICOS framework

PICOS: population, intervention, comparator, outcomes, study design; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; BEC: blood eosinophil count; CT: computed tomography

Information Sources and Search Strategy

PubMed/MEDLINE was searched from inception to November 4, 2026. The search was supplemented by Google Scholar, additional free-text PubMed strings, and backward and forward citation screening of the included studies and of relevant reviews identified during the search. All searches were last run on November 4, 2026.

The primary search string was: bronchiectasis AND eosinophil* AND (inhaled corticosteroid* OR fluticasone OR budesonide OR beclomethasone). A complementary string restricted to titles and abstracts was: bronchiectasis[Title] AND (inhaled corticosteroid*[Title/Abstract] OR inhaled steroid*[Title/Abstract] OR ICS[Title/Abstract]) AND (eosinophil*[Title/Abstract] OR type 2[Title/Abstract] OR biomarker*[Title/Abstract]). Supplementary strings combined bronchiectasis and ICS terms with exacerbation, pneumonia, mortality, Pseudomonas, cohort, registry, and post hoc terms. No language filter was applied at the search stage. The complete supplementary PubMed strings, the Google Scholar queries and screening limits, and the citation-searching procedure are reported in Appendix B.

Study Selection and Data Extraction

Records were de-duplicated manually by PubMed identifier, digital object identifier, and title and screened in two stages. Titles and abstracts were screened first, followed by full-text assessment of potentially eligible reports against the PICOS criteria. Screening and eligibility assessment were performed by two reviewers independently, and disagreements were resolved by discussion. Reasons for full-text exclusion were recorded and are reported in Appendix C.

Two reviewers independently extracted data using a standardized form: first author, publication year, country and setting, study design, population and sample size, comorbid airway disease, ICS exposure, comparator, BEC thresholds and timing, outcomes, follow-up, adjustment strategy, and effect estimates within each BEC stratum, together with the reference group of each estimate, the type of effect measure, and any reported test of interaction. Estimates were extracted from the full text, including tables and supplementary material. When values in the abstract and the full text differed, the full-text value was used after verification against the relevant table or supplementary file, and each discrepancy was documented. Re-examination during revision showed that the exacerbation values reported in one study represented changes after ICS treatment rather than between-group differences, and they are reported accordingly.

Risk-of-Bias Assessment

Risk of bias was assessed with the Newcastle-Ottawa Scale (NOS) [17], using the cohort version for cohort and matched-exposure designs and the case-control version for nested case-control analyses. Two reviewers performed the assessments independently, and disagreements were resolved by discussion. Studies were scored across selection (maximum four stars), comparability (maximum two stars), and outcome or exposure

(maximum three stars) domains. Total scores of 7-9 were considered good quality, 5-6 moderate quality, and ≤4 poor quality. Item-level judgments with supporting explanations are provided in Appendix D.

Data Synthesis

Because the included studies differed in eosinophil thresholds (percentage-based, absolute, and laboratory upper limit of normal), comparators, outcomes, and effect measures (odds ratios, hazard ratios, relative risks, and regression coefficients), a meta-analysis was not considered appropriate. Results were synthesized narratively, grouped by outcome domain (exacerbations; infection-related and lung function outcomes) and, within each domain, by population: bronchiectasis without ICS-responsive comorbidities, bronchiectasis-COPD overlap or bronchiectasis with airflow obstruction, and general bronchiectasis cohorts in which COPD was not an exclusion criterion.

For each study, the adjusted estimate for the ICS comparison within each BEC stratum was selected as the primary estimate; descriptive values were used only when no adjusted estimate was reported. Each estimate was classified by the evidence it provides for effect modification: a formally tested ICS-by-BEC interaction; stratum-specific estimates without an interaction test; a data-derived optimal threshold; or a comparison of eosinophilic ICS users with a common reference group, which does not isolate a within-stratum treatment effect. A significant estimate in one stratum and a non-significant estimate in another were not regarded as sufficient evidence of effect modification. Where ratio estimates with 95% CIs were reported for the same comparison in two or more BEC strata, the difference between strata was examined with the approximate test of interaction described by Altman and Bland, using log-transformed estimates, standard errors derived from the reported CIs, and an assumption of independent strata [18]; when a published 95% CI was not symmetric around its point estimate on the log scale, the test was repeated with the standard error derived from each bound separately and the resulting range is reported. These reviewer-derived tests were exploratory and unadjusted for multiplicity, and are reported as ratios of estimates with 95% CIs and P values; non-significant results were not interpreted as evidence of no effect. Post hoc analyses of randomized trials published as research letters, which did not meet the design criterion, were summarized separately as supportive evidence and were not combined with the included studies. Results are presented in summary tables, a non-pooled forest plot of reported adjusted estimates, and an evidence map of the direction of effect modification.

Results

Study Selection

The database search yielded 99 records, of which 26 were duplicates across search strings. After screening 73 titles and abstracts, 18 reports were assessed in full text, and 11 were excluded: 4 were short-format reports or letters, 3 did not report an ICS-by-BEC analysis, and 4 enrolled ineligible populations. Six further reports identified through supplementary searching were assessed and excluded because they did not stratify ICS effects by BEC (n = 5) or evaluated systemic rather than inhaled corticosteroids (n = 1). Seven studies were therefore included (Figure *1*). All four short-format reports were post hoc analyses of randomized trials published as research letters; they are summarized separately below, and reasons for exclusion are also listed.

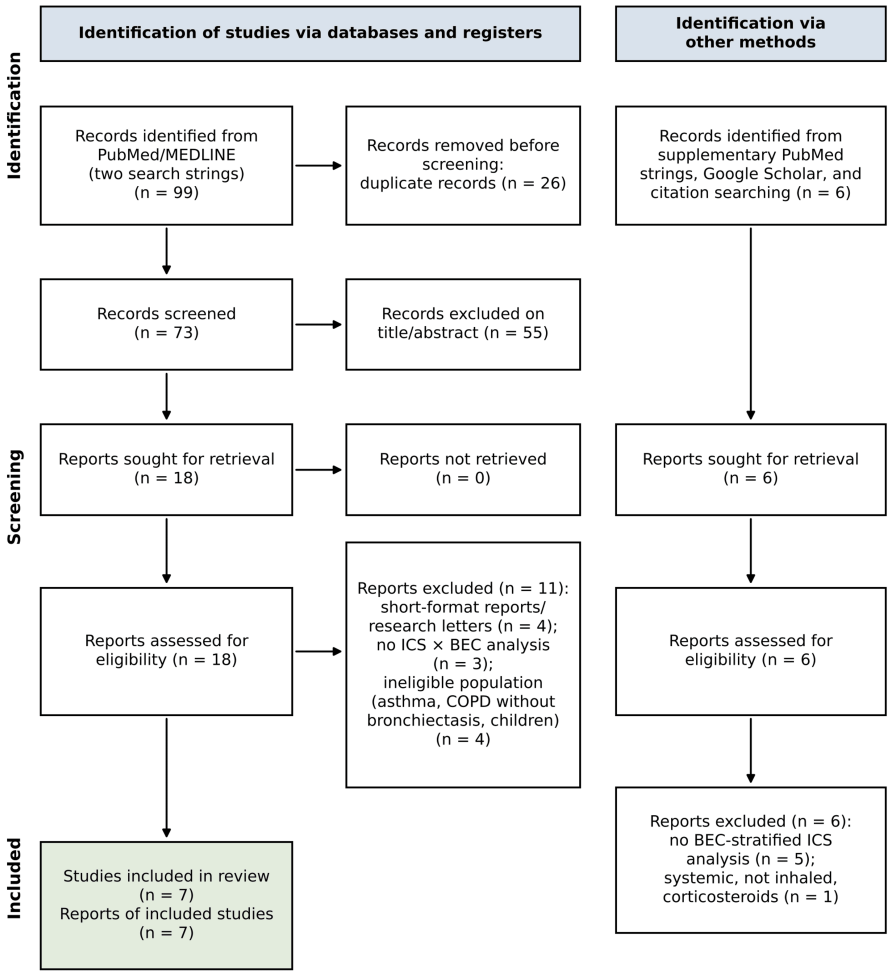


FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ICS: inhaled corticosteroids; BEC: blood eosinophil count; COPD: chronic obstructive pulmonary disease

Characteristics of Included Studies

The seven included studies were published between 2023 and 2026 (Table *2*) [19-25]. Three were prospective registry or cohort analyses [19,21,24], three were retrospective cohort studies [20,23,25], one of which compared ICS users with 1:1 matched non-users and was labelled a case-control study by its authors [20], and one was a population-based cohort with a nested case-control analysis [22]. Studies originated from Spain [19,21], Hong Kong [20], the United Kingdom [22], South Korea [23], mainland China [25], and a 31-country European registry [24]. The eosinophil-stratified analytic samples ranged from 115 to 4,385 patients. For the synthesis, two studies analyzed bronchiectasis after excluding both asthma and COPD [20,24]; three analyzed bronchiectasis-COPD overlap or bronchiectasis with airflow obstruction [21-23]; and two analyzed general bronchiectasis cohorts in which COPD was not an exclusion criterion, one of which excluded asthma [19,25]. Eosinophil thresholds varied considerably and included 300 cells/µL [19,21-23,25], a blood eosinophil percentage of 3.5% [20], and the local laboratory upper limit of normal (typically >400-500 cells/µL) [24]. All studies used a single baseline or pre-treatment BEC, and none was a randomized trial. Formal ICS-by-BEC interaction tests were reported inconsistently and were not available for most extracted estimates; the evidence for effect modification therefore consisted mainly of stratum-specific estimates, a data-derived threshold [20], or a common-reference comparison [24] (Tables *3*, *4*).

Study	Country/Setting	Design	Population (n)	ICS Exposure vs Comparator	BEC strata
Bronchiectasis without ICS-responsive comorbidities					
Kwok 2023 [20]	Hong Kong; tertiary center	Retrospective 1:1 exposure-matched cohort (authors: case-control)	Bronchiectasis without asthma or COPD (140; 70 ICS)	Regular ICS ≥12 months vs matched non-users	Percentage cut-offs (optimal ≥3.5%); absolute 100–300/μL
Pollock 2025 [24]	31 countries (EMBARC registry)	Prospective multinational registry cohort	19,324 with bronchiectasis; 4,385 without asthma/COPD/ABPA with BEC data	Eosinophilic ICS users vs non-eosinophilic ICS non-users (common reference)	> local ULN (typically >400–500/μL)
Bronchiectasis–COPD overlap or airflow obstruction					
Oscullo 2023 [21]	Spain; two outpatient clinics	Post hoc analysis of prospective cohort	GOLD II–IV COPD with bronchiectasis (115; 84 ICS)	ICS vs no ICS	<100, 101–300, >300/μL
Ritchie 2023 [22]	UK; CPRD Aurum linked to HES	Population cohort with nested case-control	COPD–bronchiectasis overlap (521 cases, 2,006 controls)	ICS vs no ICS (new-user design)	≤300, >300/μL
Lee 2024 [23]	South Korea; single center	Retrospective cohort	Bronchiectasis with FEV1/FVC <0.7 (179)	ICS/LABA/LAMA (58) and ICS/LABA (52) vs LABA/LAMA (69)	Subgroups including <200 and ≥300/μL
General bronchiectasis cohorts (COPD not excluded)					
Martínez-García 2023 [19]	Spain; 43 centers (RIBRON registry)	Prospective multicenter registry cohort	Bronchiectasis; asthma excluded, COPD not excluded (928)	ICS vs no ICS	<50, 50–100, 100–300, >300/μL
Wang 2026 [25]	China; Shanghai, multicenter	Retrospective cohort	Bronchiectasis (719; 194 ICS)	ICS vs no ICS	<100, 100–299, ≥300/μL

TABLE 2: Characteristics of the included studies, grouped by population

ABPA: allergic bronchopulmonary aspergillosis; BEC: blood eosinophil count; COPD: chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; EMBARC: European Bronchiectasis Registry; FEV1/FVC: forced expiratory volume in one second/forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HES: Hospital Episode Statistics; ICS: inhaled corticosteroids; LABA/LAMA: long-acting β2-agonist/muscarinic antagonist; RIBRON: Spanish Bronchiectasis Registry; ULN: upper limit of normal

Study	High-BEC Definition	Comparison (Reference)	Estimate in High-BEC Stratum (95% CI)	Overall or Lower Strata	Evidence Type
Bronchiectasis without ICS-responsive comorbidities					
Kwok 2023 [20]	≥3.5%	Regular ICS vs matched non-users	aOR 0.138 (0.023–0.822)	Overall aOR 0.461 (0.225–0.945); no absolute-count cut-off	Data-derived threshold
Pollock 2025 [24]	>ULN	Eosinophilic ICS users vs non-eosinophilic non-users	Exacerbations RR 0.70 (0.59–0.84); hospitalization RR 0.56 (0.35–0.90); mortality HR 0.62 (0.23–2.41)	Overall: no reduction in exacerbations or hospitalization	Common reference; not a within-stratum ICS effect
Bronchiectasis–COPD overlap or airflow obstruction					
Oscullo 2023 [21]	>300/μL	Change with ICS treatment	Annual exacerbations 1.77 → 1.08; severity 0.67 → 0.35	No significant change	Stratum-specific; descriptive
Lee 2024 [23]	≥300/μL	ICS-containing therapy vs LABA/LAMA	Triple: aHR 0.137 (0.034–0.553); ICS/LABA: aHR 0.196 (0.045–0.861)	Overall: aHR 0.692 (triple) and 0.491 (ICS/LABA), both NS	Subgroup estimate; no interaction test
General bronchiectasis cohort (COPD not excluded)					
Martínez-García 2023 [19]	>300/μL	ICS vs no ICS	Fewer and less severe exacerbations (significant)	No significant reduction	Stratum-specific; no interaction test

TABLE 3: Exacerbation outcomes by blood eosinophil stratum, with comparator and type of evidence for effect modification

Estimates are presented as reported; odds ratios, hazard ratios, and relative risks are not interchangeable. aHR: adjusted hazard ratio; aOR: adjusted odds ratio; BEC: blood eosinophil count; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; NS: not significant; RR: relative risk; ULN: upper limit of normal

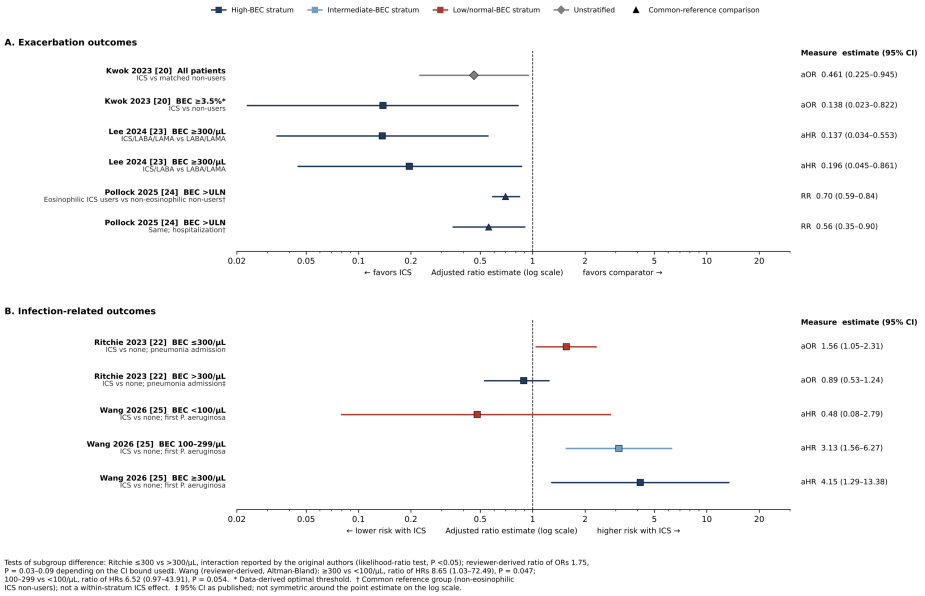
Study	Outcome (Comparison)	Lower-BEC Stratum	Higher-BEC Stratum	Test of Subgroup Difference	Interpretation
Ritchie 2023 [22]	Hospitalized pneumonia (ICS vs none)	≤300/μL: aOR 1.56 (1.05–2.31)	>300/μL: aOR 0.89 (0.53–1.24)†	Original authors: interaction P <0.05 (likelihood-ratio test). Reviewer-derived: ROR 1.75; P = 0.03–0.09†	Harm at lower BEC; strength of stratum difference uncertain
Lee 2024 [23]	Annual FEV1 change (ICS/LABA vs LABA/LAMA)	<200/μL: β −197 mL/year (−307 to −87)	≥300/μL: no significant difference	Not estimable	Harm observed only at lower BEC
Wang 2026 [25]	First *Pseudomonas aeruginosa* isolation (ICS vs none)	<100/μL: aHR 0.48 (0.08–2.79)	100–299/μL: aHR 3.13 (1.56–6.27); ≥300/μL: aHR 4.15 (1.29–13.38)	High vs low: RHR 8.65 (1.03–72.49); P = 0.047. Intermediate vs low: RHR 6.52 (0.97–43.91); P = 0.054	Harm in intermediate and high BEC
Oscullo 2023 [21]	Pneumonia, chronic bronchial infection, mortality	Not reported as harm	>300/μL: no increase with ICS	Not estimable	No harm detected in eosinophilic patients

TABLE 4: Infection-related and lung function outcomes by blood eosinophil stratum, with reviewer-derived tests of subgroup difference

Tests of subgroup difference were derived by the reviewers using the Altman and Bland method, assuming independent strata, and are exploratory. †Published 95% CI not symmetric on the log scale; P range uses the standard error from each bound. aHR: adjusted hazard ratio; aOR: adjusted odds ratio; BEC: blood eosinophil count; FEV1: forced expiratory volume in one second; ICS: inhaled corticosteroids; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; ROR: ratio of odds ratios; RHR: ratio of hazard ratios

Blood Eosinophils and ICS Effects on Exacerbations

Five studies assessed exacerbations, and in each, ICS use was associated with fewer exacerbations in patients with higher BEC but not in lower strata; no study formally tested the difference between strata (Table *3*; Figures *2*, *3*).



Tests of subgroup difference: Ritchie ≤300 vs >300/μL, interaction reported by the original authors (likelihood-ratio test, P <0.05); reviewer-derived ratio of ORs 1.75, P = 0.03–0.09 depending on the CI bound used‡. Wang (reviewer-derived, Altman-Bland): ≥300 vs <100/μL, ratio of HRs 8.65 (1.03–72.49), P = 0.047; 100–299 vs <100/μL, ratio of HRs 6.52 (0.97–43.91), P = 0.054. * Data-derived optimal threshold. † Common reference group (non-eosinophilic ICS non-users); not a within-stratum ICS effect. ‡ 95% CI as published; not symmetric around the point estimate on the log scale.

FIGURE 2: Study-level adjusted estimates of inhaled corticosteroid effects by blood eosinophil stratum: (A) exacerbation outcomes; (B) infection-related outcomes

Estimates are shown as reported by each study on a logarithmic scale and were not pooled because thresholds, comparators, and effect measures differed; each row states its comparator and effect measure. The Pollock estimates compare eosinophilic ICS users with non-eosinophilic non-users and do not represent a within-stratum ICS effect. Tests of subgroup difference (the original authors' interaction test for Ritchie et al. and reviewer-derived Altman-Bland tests) are shown beneath panel B; the published 95% CI for Ritchie et al. at >300/μL is plotted as reported (‡). The FEV1 regression coefficient (Table 4) is not a ratio measure and is not plotted. The dashed line indicates no effect. aHR: adjusted hazard ratio; aOR: adjusted odds ratio; BEC: blood eosinophil count; ICS: inhaled corticosteroids; LABA: long-acting β2-agonist; LAMA: long-acting muscarinic antagonist; RR: relative risk; ULN: upper limit of normal

Source: [20-25]

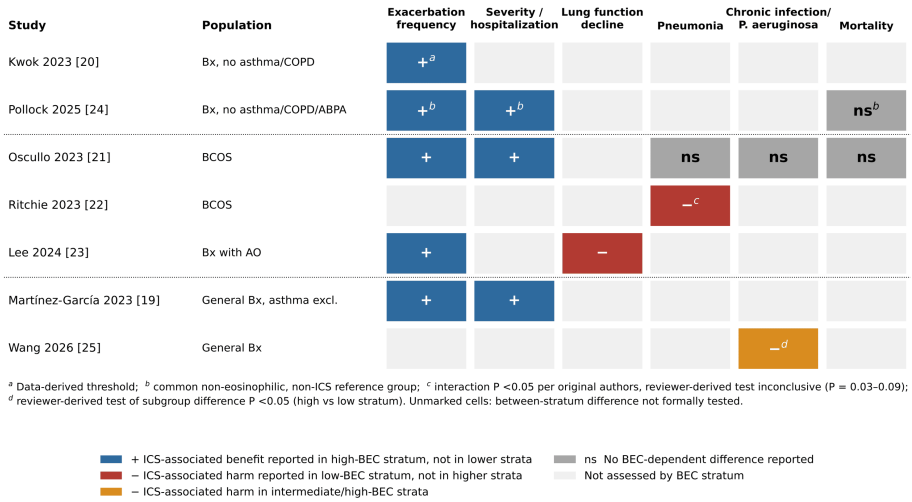


FIGURE 3: Evidence map of the direction of blood eosinophil-dependent modification of inhaled corticosteroid effects across outcome domains

Cells indicate the direction of findings across BEC strata, not formally tested effect modification. Studies are grouped by population (dotted lines): bronchiectasis without asthma or COPD; bronchiectasis-COPD overlap or airflow obstruction; and general bronchiectasis cohorts in which COPD was not excluded. Superscripts denote the type of evidence: a, data-derived threshold; b, comparison with a common non-eosinophilic, non-ICS reference group; c, interaction reported as significant by the original authors (P <0.05), with an inconclusive reviewer-derived test (P = 0.03-0.09); d, reviewer-derived test of subgroup difference P <0.05 (high vs low stratum); unmarked cells, difference between strata not formally tested. ABPA: allergic bronchopulmonary aspergillosis; AO: airflow obstruction; BCOS: bronchiectasis-COPD overlap; Bx: bronchiectasis; COPD: chronic obstructive pulmonary disease. BEC: blood eosinophil count; ICS: inhaled corticosteroids; ns: no BEC-dependent difference reported

Source: [19-25]

Bronchiectasis without ICS-responsive comorbidities: In a Hong Kong exposure-matched cohort of 140 patients without asthma or COPD, regular ICS use was associated with fewer exacerbations overall (adjusted odds ratio (aOR) 0.461; 95% CI 0.225-0.945), and a baseline eosinophil percentage of ⩾3.5% was the optimal cut-off for identifying ICS benefit (aOR 0.138; 95% CI 0.023-0.822), whereas no absolute-count cut-off between 100 and 300 cells/μL predicted response [20]. Because this threshold was selected from the same data and the estimate was imprecise, it is susceptible to overfitting and requires external validation. In the European Bronchiectasis Registry (EMBARC), ICS use was not associated with fewer exacerbations overall; among 4,385 patients without asthma, COPD, or allergic bronchopulmonary aspergillosis who had eosinophil data, ICS users with eosinophilia had fewer exacerbations (relative risk (RR) 0.70; 95% CI 0.59-0.84) and fewer hospitalizations (RR 0.56; 95% CI 0.35-0.90) than non-eosinophilic ICS non-users, with no significant difference in mortality [24]. Because both eosinophilia and ICS differ from this common reference group, these estimates do not represent the effect of ICS within the eosinophilic stratum.

Bronchiectasis-COPD overlap and airflow obstruction: In 115 patients with bronchiectasis-COPD overlap followed for a median of 74 months, ICS-treated patients with >300 eosinophils/μL showed a decrease in the annual number (from 1.77 to 1.08) and severity (from 0.67 to 0.35) of exacerbations, with no significant change in lower strata; these were within-group changes rather than adjusted between-group contrasts [21]. Among 179 Korean patients with bronchiectasis and airflow obstruction, ICS/long-acting β2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) therapy (adjusted hazard ratio [aHR] 0.137; 95% CI 0.034-0.553) and ICS/LABA therapy (aHR 0.196; 95% CI 0.045-0.861) reduced moderate-to-severe exacerbations compared with LABA/LAMA only in the subgroup with BEC ⩾300 cells/μL, whereas overall comparisons were not significant [23]. The wide confidence intervals indicate few events in this subgroup, and the active bronchodilator comparator must be considered when interpreting these estimates.

General bronchiectasis cohorts: In the Spanish bronchiectasis registry (n = 928), which excluded asthma but not COPD, BEC showed a U-shaped relationship with disease severity, and ICS use was associated with fewer and less severe exacerbations only in patients with >300 eosinophils/μL, who represented 16.5% of the cohort; no interaction test was reported [19]. Because patients with coexisting COPD were not excluded, part of this association may reflect an established ICS indication.

Blood Eosinophils and Infection-Related and Lung Function Outcomes

Four studies reported infection-related or lung function outcomes by BEC stratum (Table 4). In a UK population-based nested case-control analysis of COPD-bronchiectasis overlap (521 cases and 2,006 matched controls with recent BEC), ICS use was associated with hospitalized community-acquired pneumonia when BEC was ⩽300 cells/μL (aOR 1.56; 95% CI 1.05-2.31), but not when it was >300 cells/μL (aOR 0.89; 95% CI 0.53-1.24) [22]. On verification against the original article, these values match the published abstract and results; however, the published 95% CI for the >300 cells/μL stratum is not symmetric around 0.89 on the log scale, and the corresponding text in the results section reports a CI for the ⩽300 cells/μL stratum (0.78-1.41) that excludes its own point estimate, indicating a reporting error in the source. The original authors reported a significant ICS-by-BEC interaction (likelihood-ratio test, P <0.05) without an exact P value or interaction estimate. Our recalculated test gave a ratio of odds ratios of 1.75, with P = 0.09 (95% CI 0.91-3.36) when the standard error was derived from the lower bound and P = 0.03 (95% CI 1.05-2.93) when derived from the upper bound; the strength of this stratum difference is therefore uncertain. In the Korean cohort, ICS/LABA was associated with an accelerated annual decline in forced expiratory volume in one second (FEV1) compared with LABA/LAMA in patients with BEC <200 cells/μL (adjusted β −197 mL/year; 95% CI −307 to −87) [23]. In contrast, a multicenter Chinese cohort of 719 patients found that ICS use was associated with a higher risk of first *Pseudomonas* (*P.) aeruginosa* isolation in patients with intermediate BEC (100-299 cells/μL; aHR 3.13; 95% CI 1.56-6.27) and high BEC (⩾300 cells/μL; aHR 4.15; 95% CI 1.29-13.38), but not in patients with BEC <100 cells/μL (aHR 0.48; 95% CI 0.08-2.79); propensity-matched analyses supported these findings [25]. The difference between the high and low strata was of borderline significance (ratio of hazard ratios 8.65; 95% CI 1.03-72.49; P = 0.047), as was that between the intermediate and low strata (6.52; 95% CI 0.97-43.91; P = 0.054), and the estimates were very imprecise. In the overlap cohort, ICS benefit in eosinophilic patients occurred without a detectable increase in pneumonia, chronic bronchial infection, or mortality [21].

Trial-Derived Post Hoc Analyses (Supportive Evidence)

Four post hoc analyses of randomized trials, excluded from the primary synthesis because they were published as research letters, were examined separately. They derive from a small number of trials conducted by overlapping investigator groups, and the pooled analysis of two trials overlaps with the single-trial analyses; they therefore cannot be counted as independent evidence. In a fluticasone trial, six months of treatment improved quality of life in patients with a baseline blood eosinophil percentage of ⩾3%, a threshold chosen because it was the cohort median [11]. The pooled analysis suggested fewer exacerbations with ICS in patients with blood eosinophilia [12], and an analysis that also examined the repeatability of eosinophil measurements reported reductions in the number and severity of exacerbations among ICS-treated patients with peripheral eosinophilia [26]. In contrast, an analysis of an inhaled budesonide trial found that blood eosinophils did not predict response [13]. The trial-derived evidence is therefore directionally similar to the observational findings but small, overlapping, and not uniformly concordant.

Risk of Bias

On the NOS, four studies were of good quality [20-22,24] and three were of moderate quality [19,23,25] (Table 5; item-level judgments in Appendix E). The main concerns were confounding by indication because ICS users generally had more severe disease, reliance on a single BEC measurement, limited reporting of follow-up completeness, and, in single-center studies, restricted representativeness. Only some studies used multivariable adjustment or matching that addressed disease severity, and formal ICS-by-BEC interaction tests were rarely reported.

Study	NOS version	Selection (/4)	Comparability (/2)	Outcome or exposure (/3)	Total (/9)	Quality
Martínez-García 2023 [19]	Cohort	★★★	★	★★	6	Moderate
Kwok 2023 [20]	Cohort (matched)	★★★	★★	★★	7	Good
Oscullo 2023 [21]	Cohort	★★★	★	★★★	7	Good
Ritchie 2023 [22]	Case-control	★★★★	★★	★★	8	Good
Lee 2024 [23]	Cohort	★★	★★	★★	6	Moderate
Pollock 2025 [24]	Cohort	★★★	★★	★★	7	Good
Wang 2026 [25]	Cohort	★★★	★★	★	6	Moderate

TABLE 5: Risk-of-bias assessment using NOS

Each star represents one item satisfied. Total scores of 7-9 indicate good quality, 5-6 moderate quality, and ≤4 poor quality.

NOS: Newcastle-Ottawa Scale

Discussion

Principal Findings

This systematic review identified seven peer-reviewed observational studies, published between 2023 and 2026, that examined whether BEC modifies the effects of ICS in adults with bronchiectasis. Three findings emerged. First, in every study that analyzed exacerbations, ICS use was associated with fewer exacerbations in patients with elevated eosinophil counts but not in lower strata, whether eosinophilia was defined as ⩾300 cells/μL, ⩾3.5%, or above the laboratory upper limit of normal, and across different health systems, designs, and populations [19-21,23,24]. Second, low eosinophil counts identified patients in whom ICS were associated with pneumonia and accelerated lung function decline [22,23]. Third, eosinophilia did not appear to protect against ICS-associated *P. aeruginosa* acquisition [25]. However, a consistent direction is not the same as demonstrated effect modification. Formal interaction evidence was sparse; the tests of subgroup difference that could be performed were borderline or, for pneumonia, uncertain because of an internally inconsistent published CI; one threshold was data-derived; and the largest study compared eosinophilic ICS users with a common reference group. BEC is therefore best regarded as a candidate predictor of ICS efficacy supported by consistent but indirect evidence, and not as a sufficient predictor of ICS safety.

Comparison With Previous Evidence and Biological Plausibility

These observational findings are consistent with hypothesis-generating post hoc analyses of earlier randomized trials, which suggested improved quality of life and fewer exacerbations with ICS in patients with blood eosinophilia [11,12,26], although an analysis of a budesonide trial did not [13]. Differences in ICS molecule, dose, trial duration, and the very small number of eosinophilic participants may explain this discrepancy. Because randomization reduces confounding by indication, which is the main threat to validity in the included studies, the directional agreement between trial-derived and observational signals is relevant, but the overlapping trial populations limit its weight. It is plausible that the neutral overall results of ICS trials summarized in the Cochrane review [5] partly reflect dilution of a real effect in a responsive minority by a larger non-responsive or harmed majority. Prospective randomized data remain scarce: the only recent placebo-controlled trial with an ICS-containing arm, the Dual Bronchodilators in Bronchiectasis Study (DIBS), was stopped early after 33 participants had been randomized and could not address eosinophil-specific effects [27,28].

The biological rationale for this pattern is plausible. Eosinophilic inflammation is present in approximately one in five patients with bronchiectasis even after asthma is excluded, and elevated eosinophil counts are associated with exacerbations once infection status is accounted for [7]. Corticosteroids are particularly effective against eosinophilic, type 2-driven inflammation, whereas the neutrophilic and infection-driven inflammation that predominates in most patients, reflecting the heterogeneity of underlying endotypes [1], responds poorly to them [6]. In the EMBARC-BRIDGE study, airway eosinophil protein concentrations correlated only moderately with BEC ($r = 0.33$), and eosinophilic bronchiectasis was associated with distinct microbiological and sensitization features [29]. BEC is therefore an imperfect surrogate for airway eosinophilic inflammation, and mismatches between blood and airway compartments may contribute to heterogeneity in ICS response.

Low Eosinophil Counts and Infection-Related Outcomes

The Spanish registry demonstrated a U-shaped relationship in which eosinopenic patients had the most severe disease, the most exacerbations, and a more adverse microbiological profile [19], consistent with earlier phenotypic clustering [8], and in Hong Kong a stable-state BEC below 250 cells/µL predicted hospitalized exacerbations [30]. In COPD, low eosinophil counts combined with chronic bronchial infection identified patients in whom ICS increased pneumonia risk [9], and the UK overlap analysis extended this observation to COPD-bronchiectasis overlap [22], although the strength of this stratum difference is uncertain, because the original interaction test was reported only as $P < 0.05$ and our recalculation was inconclusive. A recent study of hospitalized patients with COPD-bronchiectasis overlap found that systemic corticosteroids were associated with higher in-hospital mortality when admission BEC was low, particularly below 100 cells/µL [31]. Because that study concerned short-term systemic corticosteroids during hospitalization, it provides only indirect context for maintenance ICS and does not inform ICS effects directly. Taken together, these data raise concern about ICS use in patients with persistently low eosinophil counts, but they do not establish any threshold below which ICS should be withdrawn.

The *P. aeruginosa* finding requires careful interpretation [25]. ICS use was associated with a three- to four-fold higher risk of first isolation in patients with intermediate or high BEC, whereas no excess risk was seen in the lowest stratum. This contrasts with the pneumonia data, in which harm was concentrated in low-BEC patients [22], and with the overlap cohort, in which ICS benefit in eosinophilic patients was not accompanied by more chronic bronchial infection [21]. The low-BEC stratum was small and its estimate imprecise; patients with low BEC may already have a high background prevalence of established infection, leaving fewer patients at risk of a first isolation; and confounding by indication may differ across strata. Independent of BEC, other cohorts have linked ICS, particularly at high doses, to a higher prevalence of *P. aeruginosa* and higher all-cause mortality [32] and to a higher risk of *Staphylococcus aureus* isolation [33]. BEC may therefore predict who benefits from ICS without predicting who will avoid microbial complications, and microbiological surveillance should accompany any ICS use in eosinophilic patients.

Definition of Eosinophilia and Methodological Considerations

The included studies used a percentage threshold of 3.5% [20], an absolute threshold of 300 cells/µL [19,21-23,25], and laboratory-specific upper limits of normal [24], and all classified patients using a single measurement. Longitudinal registry data show that reliability between consecutive annual measurements is good but declines thereafter, and that nearly half of patients classified as eosinophilic or eosinopenic change category over subsequent years [34]; patients with persistent eosinophilia also have greater severity and more frequent and severe exacerbations than those with transient eosinophilia [35]. Non-differential misclassification would generally bias effect modification toward the null, but it may also obscure subgroups in whom eosinophilia, and therefore ICS benefit, is transient. Several further features limit causal interpretation. Multiple strata and outcomes were examined without correction for multiplicity, and some thresholds were selected from the same data, which favors chance findings and overestimates subgroup effects. Prevalent-user and registry designs include patients who have already remained on ICS and are therefore survivors of the early treatment period; when risk varies over time, this selection can bias estimates and make early harms appear smaller than they are [36]. Comparator choice also matters: in the Korean cohort, the reference group received dual bronchodilators, which may themselves reduce exacerbations in bronchiectasis with airflow limitation in observational data [37], although a randomized crossover trial of tiotropium improved FEV1 without reducing exacerbations [38]. Finally, undiagnosed asthma or unrecognized allergic bronchopulmonary aspergillosis may contribute to eosinophilia in some patients, and incomplete screening for these conditions in observational datasets may partly explain the apparent ICS benefit. That the direction of findings was similar in bronchiectasis with and without COPD supports the argument that inflammatory biomarkers may be more informative than diagnostic labels [14], and that guidance organized around comorbid diagnoses [4] may eventually need to incorporate eosinophil-based phenotyping.

Clinical Implications

The current evidence does not justify routine BEC-guided initiation or withdrawal of ICS in bronchiectasis because it is entirely observational, formal interaction evidence is limited, and thresholds have not been validated. Pending biomarker-stratified trials, the following should be regarded as hypotheses requiring validation rather than recommendations. First, in patients with frequent exacerbations despite optimized airway clearance and treatment of infection, persistent eosinophilia (for example, ⩾300 cells/µL on repeated stable-state measurements) may identify candidates for a time-limited ICS trial with predefined endpoints, preferably in specialist settings and when *P. aeruginosa* infection is absent. Second, in patients with low eosinophil counts, the included studies showed no evidence of benefit and some signals of infection-related harm, but no study tested a specific threshold for withholding or withdrawing ICS; review of ICS that lack a clear indication should therefore follow existing guidance [4] rather than a BEC cut-off. Third, when ICS are used, the lowest effective dose and regular sputum microbiology are prudent, as dose-dependent harms have been described [32,33]. These principles are consistent with the treatable-traits approach [6,14].

Research Priorities

No randomized controlled trial has prospectively stratified patients by BEC or tested an ICS-by-eosinophil interaction as a primary hypothesis. The optimal threshold, the preferred metric (absolute or percentage), and the number and timing of measurements needed to define a stable eosinophilic phenotype remain uncertain, as do the comparative effects of different ICS molecules and doses [11,13]. Outcomes beyond exacerbations, including quality of life, sputum microbiome composition, nontuberculous mycobacterial infection, and long-term lung function, have rarely been reported by eosinophil stratum. Data from Africa, South Asia, Latin America, and the Middle East are lacking, as are data on whether airway biomarkers such as sputum eosinophils, eosinophil-derived proteins, or fractional exhaled nitric oxide improve prediction beyond BEC [29]. The relationship between ICS responsiveness and response to biologics targeting type 2 inflammation should also be clarified. Adequately powered, biomarker-enriched randomized trials with repeated eosinophil measurements, systematic exclusion of type 2 comorbidities, a prespecified treatment-by-eosinophil interaction analysis, and prespecified infection-related safety outcomes are the logical next step.

Limitations

This review has several limitations. All included studies were observational, and confounding by indication is likely because ICS users generally had more severe disease; residual confounding cannot be excluded even in adjusted and propensity-matched analyses. The heterogeneity of eosinophil thresholds, comparators, outcomes, and effect measures precluded meta-analysis, so no pooled estimate could be calculated, and the forest plot presents study-level estimates only. Tests of subgroup difference could be derived for only two studies, assumed independence between strata, and relied on rounded published CIs, one of which was internally inconsistent; they are therefore approximate. Some stratum-specific estimates were based on small numbers and were imprecise. Only a single baseline BEC was available in each study, which may have caused misclassification. The primary search was limited to PubMed/MEDLINE, supplemented by Google Scholar and citation searching; Embase, Scopus, and Web of Science were not searched, so some eligible studies may have been missed. By design, letters, research letters, and short-format reports were excluded, which removed hypothesis-generating post hoc analyses of randomized trials from the formal synthesis; these are summarized separately but were not formally appraised for risk of bias. The NOS does not specifically assess the validity of subgroup or interaction analyses. Finally, publication and outcome-reporting bias cannot be excluded, because studies finding no effect modification may be less likely to report stratified analyses.

Conclusions

In adults with non-cystic fibrosis bronchiectasis, observational studies consistently reported fewer ICS-associated exacerbations and hospitalizations in patients with elevated eosinophil counts than in those with lower counts, and lower eosinophil counts were associated with signals of ICS-associated pneumonia and accelerated lung function decline. However, these patterns are largely based on comparisons of statistical significance across strata rather than tested interactions; where differences between strata could be tested, the results were borderline or uncertain. Eosinophilia did not appear to protect against ICS-associated *P. aeruginosa* acquisition. BEC is therefore a hypothesis-generating, not validated, candidate biomarker for ICS selection, and the current evidence does not support any eosinophil threshold for starting or withdrawing ICS. Until biomarker-stratified randomized trials using repeated eosinophil measurements are available, ICS should not be prescribed routinely based on BEC alone and, when used, should be accompanied by microbiological monitoring and periodic reassessment.

Appendices

Appendix A

Element	Prespecified approach	Change and timing
Eligibility	PICOS criteria in Table 1; short-format reports and letters excluded; publication-date restriction only if ≥10 studies eligible	No change; date restriction not triggered
Data extraction	Duplicate independent extraction with a standardized form	Discrepancies between abstract and full text resolved in favor of verified full-text values (previously abstract values); peer-review stage
Synthesis	Narrative synthesis by outcome domain	Grouping by population and classification of the evidence type for each estimate added; peer-review stage
Effect modification	Stratum-specific estimates summarized	Approximate Altman-Bland tests of subgroup difference added where independent stratum estimates were reported; peer-review stage
Trial-derived letters	Excluded from synthesis	Remain excluded; summarized separately as supportive evidence; peer-review stage
Risk of bias	NOS, cohort or case-control version	Item-level judgments reported (Appendix 3); reporting change only

TABLE 6: Key protocol elements and changes made after the protocol was finalized

NOS: Newcastle-Ottawa Scale; PICOS: population, intervention, comparator, outcomes, study design

Appendix B

Source	Query or procedure	Limits
PubMed/MEDLINE, string 1 (primary)	bronchiectasis AND eosinophil* AND (inhaled corticosteroid* OR fluticasone OR budesonide OR beclomethasone)	Inception to November 4, 2026; no language filter
PubMed/MEDLINE, string 2 (complementary)	bronchiectasis[Title] AND (inhaled corticosteroid*[Title/Abstract] OR inhaled steroid*[Title/Abstract] OR ICS[Title/Abstract]) AND (eosinophil*[Title/Abstract] OR type 2[Title/Abstract] OR biomarker*[Title/Abstract])	As above
PubMed/MEDLINE, supplementary string 3	bronchiectasis AND (inhaled corticosteroid* OR inhaled steroid* OR fluticasone OR budesonide OR beclomethasone) AND (exacerbation* OR pneumonia OR mortality OR Pseudomonas)	As above
PubMed/MEDLINE, supplementary string 4	bronchiectasis AND (inhaled corticosteroid* OR inhaled steroid*) AND (cohort OR registry OR "post hoc")	As above
Google Scholar	"bronchiectasis" "inhaled corticosteroids" eosinophils; "bronchiectasis" "inhaled corticosteroids" "blood eosinophil" cohort	First 100 records per query, sorted by relevance
Citation searching	Backward screening of reference lists and forward screening (Google Scholar "Cited by") of the seven included studies and of relevant reviews identified by the search	No date limit
De-duplication	Manual matching by PubMed identifier, digital object identifier, and title across all sources	Not applicable

TABLE 7: Complete search strategies

Records from strings 1 and 2 (n = 99) formed the database search in Figure 1; records from supplementary strings, Google Scholar, and citation searching not already identified were counted under other methods (n = 6).

Appendix C

Report	Source	Reason for exclusion
Aliberti 2020 [11]	Database search	Research letter (short-format report); post hoc analysis of a fluticasone trial; overlaps with the pooled analysis
Martínez-García 2020, Respir Med [12]	Database search	Short-format report; pooled post hoc analysis of two randomized trials overlapping with single-trial analyses
Martínez-García 2020, Arch Bronconeumol [26]	Database search	Research letter; post hoc analysis of a randomized trial; overlapping participants
Aliberti 2020 [13]	Database search	Research letter; post hoc analysis of a budesonide trial; overlaps with the pooled analysis
Liu 2026 [31]	Supplementary searching	Systemic, not inhaled, corticosteroids during hospitalization
Three reports	Database search	No ICS-by-BEC analysis
Four reports	Database search	Ineligible population (asthma, COPD without bronchiectasis, or children)
Five reports	Supplementary searching	ICS effects not stratified by BEC

TABLE 8: Reports assessed in full text and excluded, with reasons

BEC: blood eosinophil count; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids

Appendix D

Study	S1	S2	S3	S4	C	O1/E1	O2/E2	O3/E3	Main reason for lost stars
Martínez-García 2023 [19]	★	★	★	–	★	★	★	–	Exacerbation history present at baseline; adjustment for severity limited; follow-up completeness not reported
Kwok 2023 [20]	–	★	★	★	★★	★	★	–	Single tertiary center; follow-up completeness not reported
Oscullo 2023 [21]	–	★	★	★	★	★	★	★	Two clinics only; limited adjustment for disease severity
Ritchie 2023 [22]	★	★	★	★	★★	★	★	–	Non-response not applicable or not reported
Lee 2024 [23]	–	★	★	–	★★	★	★	–	Single center; outcome history at baseline; follow-up completeness not reported
Pollock 2025 [24]	★	★	★	–	★★	★	★	–	Exacerbation history present at baseline; registry follow-up completeness not reported
Wang 2026 [25]	–	★	★	★	★★	★	–	–	Single-city tertiary sample; variable follow-up duration; completeness not reported

TABLE 9: Item-level Newcastle-Ottawa Scale judgments with supporting explanations

Cohort version: S1 representativeness of the exposed cohort; S2 selection of the non-exposed cohort; S3 ascertainment of exposure; S4 outcome absent at start; C comparability; O1 assessment of outcome; O2 adequate follow-up length; O3 adequacy of follow-up. Case-control version (Ritchie): S1 case definition; S2 representativeness of cases; S3 selection of controls; S4 definition of controls; E1 ascertainment of exposure; E2 same method for cases and controls; E3 non-response rate.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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