The Eosinophil–Microbiome Paradox In COPD: When the Biomarker That Selects Inhaled Corticosteroids is Also Associated with Bacterial Risk

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ABSTRACT

Background: The blood eosinophil count guides inhaled corticosteroid (ICS) therapy in chronic obstructive pulmonary disease (COPD). The 2026 GOLD report adds a weaker second reading: a low count is *associated* with Proteobacteria predominance and more bacterial infection.

Objective: To grade the evidence behind each reading and set out what follows clinically.

Methods: Narrative review, not systematic. The 2026 GOLD report and its sources were primary, supplemented by PubMed/MEDLINE, Scopus and Google Scholar searches, 2016–2026. Both authors screened in two stages; each key study was appraised by design, sample size, eosinophil threshold, microbiome method and confounding, and that appraisal is tabulated.

Results: The eosinophil–ICS relationship is continuous and well established, with little benefit below 100 cells/µL. The microbiome relationship is weaker and wholly observational: the largest cohort (n=253) found Proteobacteria dominance associated with blood eosinophils at or below 100 cells/µL and with higher mortality, while a qPCR cohort found the association with *sputum* but not blood eosinophils. Two studies found none, both comparing high against non-high counts rather than the sub-100 cells/µL group underpinning the GOLD statement. DISARM shows ICS modify the microbiome, most markedly with fluticasone.

Conclusion: A low count is a validated reason to expect little ICS benefit; it is *not* a validated marker of pathogenic airway microbiota and should not be used as one. The paradox remains a hypothesis. ICS decisions must rest on exacerbation history, prior infection and guideline thresholds, not the count alone, and prospective validation is needed in high-tuberculosis-burden populations.

Keywords: COPD; blood eosinophils; airway microbiome; dysbiosis; inhaled corticosteroids; pneumonia; tuberculosis

INTRODUCTION

Over the past decade the blood eosinophil count has become the one biomarker that genuinely changed practice in chronic obstructive pulmonary disease (COPD). Its role has been single and clear: to determine who should receive an inhaled corticosteroid (ICS). The GOLD Science Committee treats it as the marker that guides the response to ICS,[1] and its thresholds are now embedded in the treatment algorithms of almost every guideline, including the 2025 update of GesEPOC.[2]

The 2026 GOLD report adds something that is seldom read closely. In its account of ICS, GOLD states that lower blood and sputum eosinophils are associated with a greater presence of Proteobacteria, notably *Haemophilus*, and with increased bacterial infections and pneumonia. The sentence that follows concludes that lower blood eosinophil counts **may** therefore identify individuals with microbiome profiles associated with an increased risk of clinical worsening due to pathogenic bacterial species.[3] The modal verb is GOLD's own, and it

carries the weight of the present review.

If that association holds, the eosinophil count no longer answers only the question "will this patient respond to ICS"; it also carries indirect information about the bacterial ecology of the airway. The two readings point in opposite directions. At the same time, the 2026 GOLD report devotes a section of its own to dysbiosis and states, on the basis of randomised evidence, that ICS use modifies the airway microbiome.[3] From this arises the paradox that is the subject of this review: the number used to select the drug may also be an indirect reading of the microbiome, while the drug it selects reshapes that microbiome.

Because the two faces of this number rest on evidence of very unequal strength, we have tried throughout to keep three categories distinct, and we ask the reader to hold them apart as well. The first is **established evidence**: the relationship between the eosinophil count and ICS response, demonstrated in randomised trials and incorporated into guidelines. The second is **observational association**: the relationship between eosinophil level and airway microbiota, derived from cross-sectional and longitudinal cohorts in which confounding cannot be excluded. The third is the **conceptual hypothesis** advanced here, that the two faces interact in a loop. Only the first supports a treatment decision on its own. The second does not yet license using a low eosinophil count as a diagnostic marker of pathogenic airway microbiota, and nothing in what follows should be read as proposing that it does.

METHODS

This article is a narrative review and does not follow a systematic review protocol; it was not registered, and no PRISMA flow diagram is presented. We describe the process below in enough detail for a reader to judge, and reproduce, how the evidence was assembled.

Sources and search

The primary source was the 2026 GOLD report together with the references it cites in its sections on dysbiosis, blood eosinophils and inhaled corticosteroids. Supplementary searches of PubMed/MEDLINE, Scopus and Google Scholar covered publications issued between January 2016 and October 2026, combining the terms "COPD", "blood eosinophils", "sputum eosinophils", "airway microbiome", "lung microbiome", "dysbiosis", "Proteobacteria", "Haemophilus", "inhaled corticosteroids", "pneumonia", "tuberculosis" and "nontuberculous mycobacteria", combined with the Boolean operators AND and OR. The reference lists of all retrieved reviews and of the GOLD report itself were screened by hand for further primary studies, and forward citation searching was performed on the two pivotal studies.

Eligibility and selection

Eligible records comprised guidelines and consensus documents, randomised controlled trials, prospective and cross-sectional cohort studies, network analyses, and systematic reviews with or without meta-analysis, published in English. Conference abstracts without a corresponding full publication, case reports, and studies conducted exclusively in asthma or bronchiectasis without a COPD stratum were excluded. Selection proceeded in two stages. Both authors first screened titles and abstracts against the eligibility criteria; records judged potentially relevant by either author were retained. Full texts were then read independently by both authors, and inclusion was agreed by discussion, with the GOLD report used as the reference point for whether a study bore on the stated association. We did not log counts of records retrieved at each stage prospectively, and we therefore do not report them; this is a limitation of the method rather than of the literature, and is restated in the Limitations section.

Data extraction and appraisal of the evidence

From each study bearing directly on the eosinophil–microbiome relationship we extracted the population and sample size, the eosinophil compartment measured (blood or sputum) and the threshold applied, the method used to assess bacteria or the microbiome, the effect estimate with its precision where one was reported, and the limitations acknowledged by the authors. No formal risk-of-bias instrument was applied, because the included studies are heterogeneous in design and no single validated tool covers guidelines, randomised trials and

microbiome cohorts together. Instead each study was graded narratively against four criteria that determine how far its finding can be carried: study design, sample size, whether the sub-100 cells/µL group central to the GOLD statement was actually represented, and the degree to which ICS exposure, antibiotic use and smoking were controlled. That appraisal is set out study by study in Table 2, and studies contradicting the central thesis were deliberately sought and are given equal space. Findings were synthesised qualitatively; no meta-analysis was attempted and none would be appropriate given the heterogeneity of microbiome methods.

RESULTS AND DISCUSSION

The First Face: Eosinophils as a Guide to Inhaled Corticosteroids

The first role of the eosinophil count is well established and rests on randomised evidence. GOLD states that the relationship between blood eosinophil count and ICS effect is continuous: no effect or only a small one at low counts, with incrementally increasing effects at higher counts. Data modelling indicates that ICS-containing regimens have little or no effect at a count below 100 cells/µL, so that threshold is used to identify patients unlikely to benefit. The threshold of 300 cells/µL marks the top of that continuous relationship and identifies patients with the greatest likelihood of benefit.[1,3]

The evidence comes in layers. A post-hoc analysis of three randomised trials showed that the eosinophil count predicts the response to budesonide,[4] while pre-specified analyses of the TRIBUTE, TRINITY and IMPACT trials showed the superiority of triple over dual therapy, with the magnitude of benefit tracking the eosinophil count.[5–7] The biological rationale is also clear: ICS act by suppressing inflammatory pathways that in a proportion of patients with COPD are indeed of type 2 character.[8]

Two qualifications belong here even on this firmer ground. The thresholds are decision aids within a continuous relationship, not biological boundaries, and guidelines apply them alongside exacerbation history rather than in place of it. So far, however, the account is tidy. The eosinophil count marks type 2 inflammation, and ICS target that pathway. The complication arises when the question is reversed: what does a *low* eosinophil count mean?

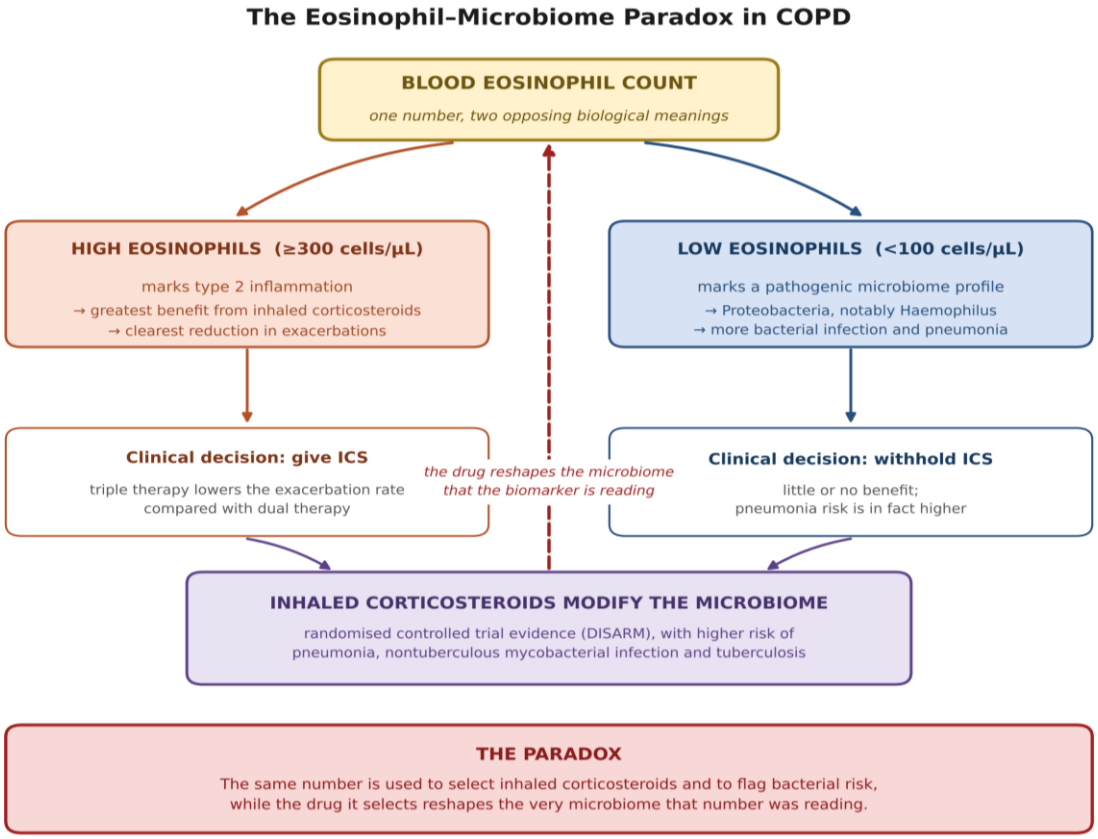

Figure 1. The proposed eosinophil-microbiome paradox in COPD. The eosinophil thresholds are established; the link with Proteobacteria is an observational association as reported in the 2026 GOLD report and the sources cited; the loop as drawn is the authors' conceptual synthesis and is not itself a validated model.[3,9,10]

The Second Face: Eosinophils as a Possible Indirect Reading of the Microbiome

To understand this second face, it is worth first being clear about what the airway microbiome is. GOLD explains that gene sequencing analysis is markedly more sensitive than the conventional cultures used in clinical practice, which detect only live bacteria colonising the airways or associated with symptoms of infection. Sequencing has shown that the lower respiratory tract is not sterile but permanently contains a diverse array of bacteria.[3] Dysbiosis refers to disruption of that microbiome and has been observed in several compartments in patients with COPD. Very diverse risk factors, such as cigarette smoking and prematurity, alter mucosal immunity and both gut and airway microbiota, which interact in both directions through the gut-lung axis.[3,11]

The evidence that the microbiome relates to clinical outcome is reasonably solid in its own right. The sputum microbiome is associated with airway inflammation and mortality in COPD,[12] lower airway dysbiosis augments lung inflammatory injury in mild-to-moderate disease,[13] and loss of airway phylogenetic diversity is associated with clinical and pathobiological markers of disease development.[14] The interplay between the microbiome and airway immunity is now regarded as one of the principal drivers of COPD pathogenesis.[15] Microbiome profiles also change after viral infection and during exacerbations,[16] and are associated with particular inflammatory endotypes over time.[17]

What the eosinophil studies actually show

The strongest single observation comes from a cohort of 253 clinically stable patients with COPD followed for a median of four years, in which sputum was characterised by 16S rRNA gene sequencing. Dominance of Proteobacteria with lower diversity was associated with more severe GOLD stage ($p=0.0015$), more frequent exacerbations ($p=0.0042$), lower forced expiratory volume in one second ($p=0.026$) and, most relevant here, a blood eosinophil count at or below 100 cells/μL ($p<0.0001$). Blood eosinophil counts were positively associated with Firmicutes and *Streptococcus* and negatively with Proteobacteria and *Haemophilus*, and Proteobacteria dominance carried a mortality hazard ratio of 2.58 (95% CI 1.43–4.66; $p=0.0017$) relative to Firmicutes dominance.[12] This is the study that most directly supports the GOLD statement, and it is observational.

A second cohort qualifies the picture in a way that matters for practice. Among 145 patients from the COPDMAP cohort with paired sputum quantitative PCR and differential cell counts, sputum eosinophil percentage was lower in those colonised with *H. influenzae* than in those with no colonisation (median 0.50% against 1.00%, $p=0.03$), a difference that persisted at six months (0.38% against 2.13%, $p=0.011$) and in the small persistently colonised subgroup. **Blood** eosinophil counts and percentages, however, showed no significant difference between colonised and non-colonised groups.[18] The association in that study therefore lies with the sputum compartment, not the blood compartment that clinicians actually measure. Since almost all practical decisions rest on a blood count, this distinction weakens the inferential chain considerably and is not, in our reading, given sufficient weight in the secondary literature.

A multicohort longitudinal analysis showed that the airway microbiome is associated with inflammatory endotype, and that a neutrophilic endotype with low eosinophils tends to be accompanied by a predominance of Proteobacteria.[17] A post-hoc analysis of a long-followed cohort including patients with bronchiectasis–COPD overlap found that those with blood eosinophils below 100 cells/μL had more infectious events, comprising exacerbations, pneumonia and chronic bronchial infection, whereas only patients above 300 cells/μL derived an exacerbation benefit from ICS.[19] A recent review states the pattern more plainly: patients with neutrophilic inflammation are more often colonised by *Haemophilus influenzae*, and that colonisation rarely coexists with eosinophilic inflammation.[20]

The biological explanation most often advanced is that eosinophils have an antibacterial role, so that low levels open the way for pathogens. The same review cautions that an antibacterial role for eosinophils in COPD is plausible but unproven, and that associations between bacteria and inflammatory profiles do not establish causation.[20] We adopt that caution as our own position. Taken together, these studies establish an association of moderate consistency between low eosinophil counts and a Proteobacteria-predominant microbiota. They do not establish that a low count identifies pathogenic colonisation in an individual patient, and no study has reported the sensitivity, specificity or predictive values that such a claim would require.

Network Analysis: Four Interconnected Nodes

One study examines the relationship between all four variables at once, using a network analysis of ICS use, circulating eosinophils, chronic airway infection and pneumonia risk in COPD.[9] The approach differs from conventional regression in that it does not force one variable to be the cause and the others the effect, but maps how all four relate to one another. The result shows that the four nodes form a single network rather than four separate findings. The design is nonetheless observational, and a network describes a structure of association; it does not resolve direction.

The finding gains context from the same group's work on chronic bronchial infection. Chronic bronchial infection, particularly with *Pseudomonas aeruginosa*, is associated with more rapid lung function decline in COPD.[21] If a microbiome profile is indeed flagged by low eosinophils, it would therefore relate not only to short-term pneumonia risk but to the rate of disease progression. That conditional is deliberate.

Table 1. The two readings of the blood eosinophil count in COPD and their opposing implications

Eosinophil level	Reading as a marker of inflammation (established)	Reading as a marker of the microbiome (observational association only)	Direction of clinical decision
< 100 cells/μL[1,3]	Minimal type 2 inflammation; little or no benefit from ICS	Associated at group level with Proteobacteria predominance, notably *Haemophilus*, and with more bacterial infection; not validated as an individual marker[12]	Both readings point the same way: ICS generally not indicated, decided with exacerbation history
100–300 cells/μL[3,4]	Intermediate zone with incrementally increasing ICS benefit	No distinctive microbiome profile described in this range	Weigh exacerbation and infection history; the count alone does not decide
≥ 300 cells/μL[3,5,7]	Prominent type 2 inflammation; greatest ICS benefit	No association with a pathogenic profile reported; one study found no microbiota difference at this threshold[22]	ICS indicated where exacerbation history supports it, with continued vigilance for infection
Change over time[3,17]	Counts may move between categories with time, exacerbation state and treatment	Microbiome profiles change after viral infection, exacerbations, antibiotics and corticosteroids	A single measurement is an inadequate basis for a long-term decision

ICS, inhaled corticosteroid.

Closing the Loop: Inhaled Corticosteroids Modify the Microbiome

The element of this paradox that rests on randomised evidence is the arrow that points back. The 2026 GOLD report states that there is high-quality randomised evidence that ICS use modifies the airway microbiome,[3] citing the DISARM trial. In that study, clinically stable patients stopped ICS during a four-week run-in on formoterol alone and were then randomised for twelve weeks to budesonide/formoterol (n=20), fluticasone/salmeterol (n=22) or formoterol alone (n=21), with bronchoscopy before and after. Changes in alpha diversity differed between groups, most clearly between fluticasone/salmeterol and formoterol alone (richness p=0.02; Shannon index p=0.03), and differential abundance shifts were more pronounced in the fluticasone arm than in the budesonide or formoterol-only arms.[10]

Two features of that trial deserve emphasis because they are often lost in citation. The effect was driven principally by fluticasone rather than budesonide, so "ICS modify the microbiome" is a generalisation from one molecule more than from a class; and with 63 patients randomised the trial was powered for a microbiological

endpoint, not a clinical one. What it establishes is that the direction ICS → microbiome exists. It does not establish the magnitude of any clinical consequence.

The consequence is nonetheless circular in structure. The eosinophil count is used to decide on ICS; part of the information that number may carry derives from the state of the microbiome; and the ICS then given alters that microbiome, at least with fluticasone. Every subsequent eosinophil measurement in a patient already receiving ICS is therefore read from a system that treatment has modified. GOLD notes that microbiome profiles are differentially altered by antibiotics and by oral and inhaled corticosteroids.[3] None of this argues that ICS should be withheld where they are indicated. It argues that an eosinophil count in an ICS-treated patient is not interchangeable with one in a patient never exposed, and that microbiome research in ICS-treated populations requires particular care in inferring direction.

The Price Paid: Pneumonia, Mycobacteria and Tuberculosis

The safety evidence is the part of the argument with the firmest footing. A patient-level meta-analysis found that the blood eosinophil count relates to pneumonia risk in COPD, with lower counts marking higher risk.[23] The SUMMIT trial and its analyses described patterns of pneumonia risk in patients with moderate airflow limitation,[24,25] and GOLD notes that a blood eosinophil count below 2% increases the risk of pneumonia independently of ICS use.[3] That last point is worth isolating: it means the pneumonia association attaches to the low count itself and not only to the drug given on account of it.

Mycobacterial risk adds a further layer that in some countries weighs more heavily than pneumonia. A systematic review and meta-analysis of non-randomised studies found an increased risk of tuberculosis among ICS users with obstructive lung disease,[26] and a nationwide population study in South Korea found an increased risk of nontuberculous mycobacterial infection among ICS users with chronic airway disease, with an adjusted hazard ratio of 4.01 (95% CI 1.48–15.58). The interval is very wide because events were few, so the point estimate should not be read as a precise quantity.[27] GOLD states that an increased risk of tuberculosis has been found in both observational studies and a meta-analysis of randomised trials.[3]

Stated carefully, the sequence runs as follows. A low eosinophil count is associated at group level with a Proteobacteria-predominant microbiota and, independently, with pneumonia risk; ICS offer this group little expected benefit; and ICS are associated with additional infectious risk. Each link is supported, the first two more securely than the inference joining them. The studies behind each link, and their individual weaknesses, are set out in Table 2.

Table 2. Structured appraisal of the principal studies bearing on the eosinophil-microbiome relationship

Study (design)	**Population**	**Eosinophil measure and threshold**	**Microbiome or bacterial assessment**	**Principal finding and effect estimate**	**Principal limitations**
Dicker 2021[12] (prospective cohort)	253 stable COPD, median 4-year follow-up	Blood; ≤ 100 cells/μL	Sputum 16S rRNA sequencing; dominance by phylum and genus	Proteobacteria dominance associated with eosinophils ≤ 100 cells/μL ($p<0.0001$); mortality HR 2.58 (1.43–4.66)	Observational; single cohort; dominance categories defined post hoc; ICS use not randomised
Beech 2020[18] (cohort analysis)	145 with paired qPCR and sputum cell counts; 226 with blood counts	Sputum % (>3% eosinophilia) and blood counts	Sputum qPCR for *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*; 16S in a subset	Sputum eosinophil % lower with *H. influenzae* (0.50% vs 1.00%, $p=0.03$); **no significant difference in blood eosinophils**	Medians and p values only, no effect sizes; high background ICS use; 34% current smokers; authors state causality not confirmed

Study (design)	Population	Eosinophil measure and threshold	Microbiome or bacterial assessment	Principal finding and effect estimate	Principal limitations
Wang 2021[17] (multicohort longitudinal)	COPD cohorts in stability and exacerbation	Blood and sputum, endotype-defined	16S rRNA sequencing	Neutrophilic, eosinophil-low endotype associated with Proteobacteria predominance	Endotype definitions vary; observational; treatment not controlled
Oscullo 2023[19] (post-hoc cohort analysis)	201 COPD, 115 with bronchiectasis overlap, median 74-month follow-up	Blood; <100, 101–300, >300 cells/µL	Serial sputum culture; chronic bronchial infection as outcome	More infectious events (exacerbations, pneumonia, chronic infection) below 100 cells/µL; ICS benefit only above 300 cells/µL	Post hoc; overlap population not generalisable to all COPD; culture rather than sequencing
Martinez-Garcia 2020[9] (network analysis)	COPD cohort with chronic bronchial infection data	Blood eosinophil count as a network node	Chronic bronchial infection by sputum culture	ICS use, eosinophils, chronic infection and pneumonia form a single network	Observational; network structure does not establish direction
Leitao Filho 2021, DISARM[10] (randomised controlled trial)	63 randomised, 56 completed; 12 weeks after a 4-week ICS washout	Not the randomisation criterion	Bronchoscopic sampling; 16S rRNA sequencing	Alpha diversity changed with fluticasone/salmeterol vs formoterol (richness p=0.02; Shannon p=0.03); budesonide arm less affected	Small; microbiological rather than clinical endpoint; effect mainly attributable to fluticasone
Perotin 2024[22] (cross-sectional) — **contradicting**	59 stable COPD, RINNOPARI cohort	Blood; above vs below 300/mm³	Airway microbiota sequencing; composition, load, alpha diversity	No difference in composition, bacterial load, alpha diversity or dominant phylum	Small; stable state only; compares high vs non-high, so the <100 cells/µL group is not isolated
Yatera 2025, AERIS-J[28] (prospective cohort) — **contradicting**	63 Japanese COPD with moderate airflow limitation	Blood and sputum eosinophils	Sputum microbiome sequencing; potentially pathogenic organisms	Diversity correlated with basophils and CAT score, not with eosinophils; pathogens did not alter diversity	Small; exploratory; single-country; the <100 cells/µL group not analysed separately

CAT, COPD Assessment Test; HR, hazard ratio; ICS, inhaled corticosteroid; qPCR, quantitative polymerase chain reaction. Effect estimates are reproduced as published; blank cells indicate that the item was not reported.

Evidence That Does Not Support the Thesis, and Why It Matters

Scientific honesty requires that contrary evidence be presented with equal weight. At least two studies did not find the expected relationship. A study of 59 patients with stable COPD from the RINNOPARI cohort compared groups with blood eosinophils below and above 300/mm³ and found no difference in airway microbiota composition, bacterial load per sample, alpha diversity or dominant phylum. The high-eosinophil group did in fact exacerbate more often and had more prominent cough and sputum production, but this was not accompanied by a distinctive microbiota profile.[22]

A prospective cohort study of 63 patients with COPD in Japan pointed the same way. Lower microbial diversity was associated with lower blood basophil counts and worse CAT scores, but showed no correlation with blood or sputum eosinophils. The presence of potentially pathogenic organisms also left alpha and beta diversity unchanged.[28]

Three explanations appear plausible, and they are not mutually exclusive. Both studies were small and sampled only in the stable state, so they may have been underpowered for a subtle difference. Both compared high eosinophils against not-high eosinophils, whereas the GOLD statement concerns **low** eosinophils, below 100 cells/μL, a group neither study isolated. And the methods used to assess the microbiome differed between studies, which is known to affect results. These are reasons why the negative findings may not refute the hypothesis; they are not reasons to discount the findings. The honest summary is that the GOLD statement is a partially supported hypothesis, and that the studies designed to test it directly have not yet been done.

Confounding, Temporal Variability and the Limits of Inference

Three problems stand between the association described above and any clinical use of it, and each deserves naming.

The first is confounding by indication and by exposure. ICS use is not randomised in any of the observational studies, and ICS are themselves prescribed on the basis of the eosinophil count, alter the microbiome,[10] and raise infection risk.[23,26] Antibiotic exposure, oral corticosteroid courses, smoking status and disease severity all independently influence both the eosinophil count and the microbiota, and few studies adjust for all of them. In the COPDMAP cohort, background ICS use was high and did not differ between colonisation groups, which limits what can be inferred either way.[18]

The second is temporal variability. A blood eosinophil count is not a fixed attribute. It varies with time of day, season, exacerbation state, corticosteroid exposure and intercurrent infection, and repeated measurements in the same patient move between the categories used to make decisions. Microbiome profiles are at least as unstable, changing after viral infection and during exacerbations[16] and differing between stability and exacerbation within the same individual.[17] An association measured once between two quantities that both fluctuate is a weak basis for classifying a patient, and regression to the mean will tend to exaggerate the apparent separation between groups defined by a single extreme value.

The third is methodological heterogeneity. Sputum and bronchoscopic sampling do not yield the same communities; 16S sequencing, quantitative PCR and conventional culture answer different questions; and the choice of hypervariable region, extraction protocol and the definition of "dominance" all affect which organisms appear to predominate. Studies reporting the presence of a pathogen by qPCR[18] and studies reporting phylum-level dominance by sequencing[12] are not measuring the same thing, and pooling their conclusions, as secondary sources often do, overstates the coherence of the field.

Clinical Consequences, Carefully Stated

What follows from all this is narrower than the paradox might suggest, and we state the negative first. A low blood eosinophil count is **not** a validated indicator of pathogenic airway microbiota, should not be used to diagnose chronic bronchial infection, and should not by itself trigger microbiological investigation, antibiotic treatment or tuberculosis screening. No study has reported operating characteristics that would justify such use. What the association supports is a shift in the clinician's index of suspicion, not a new test.

Decisions about ICS must continue to rest on the full clinical picture rather than on the eosinophil count alone. GOLD and other guidelines position the count alongside exacerbation history, hospitalisation history, concomitant asthma and a history of repeated pneumonia, and that remains the governing framework.[1–3] In a patient with two or more moderate exacerbations or one hospitalisation and an eosinophil count above 300 cells/μL, ICS are indicated; in a patient with no exacerbation history and a count below 100 cells/μL, they are not, and that conclusion rests on the exacerbation history as much as on the count. Where the two conflict, the

exacerbation history generally carries more weight than a single eosinophil measurement, which should be repeated before a long-term decision is based on it.

Sputum culture in a patient with a low count is reasonable where there are independent clinical grounds, such as chronic sputum production, a previous isolate of a potentially pathogenic organism, bronchiectasis on imaging, or frequent exacerbations, and these are the same grounds on which it would be ordered without any knowledge of the eosinophil count. We are not proposing a baseline culture for every patient below 100 cells/µL, and the evidence would not support one.

ICS withdrawal deserves the same care. A low count in a patient already receiving ICS is read from a system the treatment has altered, and withdrawal decisions should follow guideline criteria and weigh the benefit the patient has actually derived, including exacerbation frequency before and during treatment, rather than being driven by the count in isolation. Where ICS are withdrawn, lung function and exacerbation frequency warrant monitoring.

Decisions about antibiotics during an exacerbation remain clinical. GOLD states that the results of procalcitonin studies conflict, so procalcitonin-based protocols cannot be recommended for deciding on antibiotics in COPD exacerbations.[3] A systematic review in hospitalised patients found no significant reduction in overall antibiotic exposure,[29] and a recent randomised trial reinforces that uncertainty.[30] The enduring criteria are increased dyspnoea, increased sputum volume and sputum purulence, together with a prior positive sputum culture during a previous exacerbation and the need for mechanical ventilation.[3]

Finally, the possibility is emerging of influencing the microbiome without antibiotics. In a randomised phase 2 trial, patients receiving the CFTR potentiator icenticaftor showed improvements in forced expiratory volume in one second together with improvement in sputum bacterial colonisation.[3,31] This is phase 2 evidence and far from routine practice, but it indicates that the microbiome may become a therapeutic target rather than only a marker. The practical implications are summarised in Table 3.

Table 3. How the microbiome dimension does, and does not, change the reading of an eosinophil count

Clinical situation	**Established practice (unchanged)**	**What the association adds**	**What it does not justify**
Eosinophils < 100 cells/µL, ICS-naive[3,18]	Little expected ICS benefit; dual bronchodilation, decided with exacerbation history	A slightly raised index of suspicion for chronic bronchial infection if other clinical features are present	Routine sputum culture or antibiotics on the basis of the count alone
Eosinophils < 100 cells/µL, receiving ICS[3,10]	Consider withdrawal per guideline criteria, weighing benefit actually derived	Awareness that the count is read from a treatment-altered system; monitor after withdrawal	Withdrawal driven by the count alone, without reviewing exacerbation history
Eosinophils ≥ 300 cells/µL with exacerbation history[5,7]	ICS indicated; triple therapy where appropriate	Continued vigilance for pneumonia and, in endemic settings, mycobacterial disease	Withholding indicated ICS because of microbiome concerns
Patients in high-tuberculosis-burden regions[3,26,27]	Guideline thresholds applied, with risk-benefit weighed individually	Explicit consideration of tuberculosis and NTM risk in the risk-benefit discussion, per national guidance	Tuberculosis screening triggered by an eosinophil count; screening follows national policy and individual risk
Exacerbation with purulent sputum[3,29,30]	Antibiotics on clinical criteria	No change	Procalcitonin or eosinophil count as the determinant

ICS, inhaled corticosteroid; NTM, nontuberculous mycobacteria.

Applicability Across Populations and Health Systems

How far these findings travel is itself an open question. The cohorts underpinning the eosinophil–microbiome association are predominantly European and North American, with one East Asian exception that was negative.[12,18,22,28] They were recruited in settings where tuberculosis is uncommon, tobacco is the dominant exposure, sequencing is available and ICS use is high. None of those conditions holds uniformly elsewhere, and each could plausibly modify the association rather than merely dilute it.

Three differences seem most consequential. Where biomass smoke rather than tobacco is the principal exposure, the inflammatory profile and the baseline microbiota may differ. Where tuberculosis is endemic, prior or latent mycobacterial disease alters airway structure and flora in ways no European cohort captures, and post-tuberculous lung disease is itself a common cause of chronic airflow obstruction. And where sputum culture is available but sequencing is not, the clinically accessible measure is categorically different from the research measure, so a finding expressed in terms of phylum dominance has no direct operational equivalent at the bedside.

The calculus of benefit and risk from ICS therefore differs by setting. In low-prevalence countries an increased tuberculosis risk is a secondary consideration; in high-burden countries it moves forward. Evidence of increased tuberculosis risk among ICS users comes from observational studies and meta-analysis,[3,26] and nontuberculous mycobacterial risk is also increased.[27] The practical response requires no new technology: vigilance for persistent or changing symptoms in ICS users, a lower threshold for sputum examination where clinically indicated, and tuberculosis assessment before long-term ICS **in accordance with national guidance and individual risk** rather than as a consequence of any laboratory value. What is needed above all is awareness that an eosinophil algorithm derived from European and North American populations carries a different epidemiological backdrop when transplanted.

As far as our search extends, no study has examined the relationship between eosinophil count, airway microbiome and mycobacterial risk in a South-East Asian population with a high tuberculosis burden. Until such work exists, the extrapolation remains untested, and that should be stated plainly to patients and colleagues rather than assumed away.

Limitations and Directions for Research

Several limitations qualify this review. Most of the evidence linking eosinophils to the microbiome is observational and much of it cross-sectional, so direction of causality cannot be established; GOLD itself states that the paucity of longitudinal and interventional data underlines the need for further research to ascertain direction and possible prognostic, diagnostic or therapeutic applications.[3] Two of the studies discussed did not find the expected relationship, and neither can be set aside.[22,28] The association reported in one key cohort lies with sputum rather than blood eosinophils,[18] and the blood compartment is the one clinicians measure. Microbiome methods are not uniform across studies, and effect estimates are frequently absent, several studies reporting only medians and p values. The randomised evidence that ICS modify the microbiome rests on a single trial of 63 patients in which the effect was driven largely by fluticasone.[10]

The review method has its own limitations. This is a narrative review without a registered protocol; records retrieved at each screening stage were not logged prospectively and are therefore not reported, and no formal risk-of-bias instrument was applied, the appraisal in Table 2 being narrative. Selection bias in the choice of sources cannot be excluded, although contradicting studies were sought deliberately. Both authors work in a high-tuberculosis-burden setting, which may have directed attention toward the mycobacterial dimension of the question.

Four research directions follow, and they are specific. First, studies comparing the microbiome of patients with eosinophils below 100 cells/μL against higher strata, since it is precisely this group on which the GOLD statement rests and precisely this group that existing studies under-represent; such a study should report sensitivity, specificity and predictive values rather than group-level differences alone. Second, longitudinal studies measuring eosinophils and the microbiome repeatedly, before and after ICS initiation, with adjustment

for antibiotic and systemic corticosteroid exposure. Third, randomised trials stratified by microbiome profile rather than by eosinophil count alone. Fourth, prospective validation in high-tuberculosis-burden populations, including patients with post-tuberculous lung disease, before any part of this framework is applied in such settings.

CONCLUSION

The blood eosinophil count has long been treated as a single marker with a single meaning. The 2026 GOLD report raises the possibility that the number carries two messages: the first, firmly established, about type 2 inflammation and the likely benefit of inhaled corticosteroids; the second, so far observational, about the bacterial ecology of the airway. In patients with low counts the two would point in opposite directions, and the treatment chosen on the strength of the first message does appear to reshape the system that generates the second, at least with fluticasone.

The two messages are not of equal standing, and the distinction is the main message of this review. The first supports a treatment decision. The second supports a hypothesis. A low eosinophil count is a validated reason to expect little benefit from ICS; it is not a validated marker of pathogenic airway microbiota, and using it as one would outrun the evidence. Some studies do not support the association at all, and the studies designed to test it directly, in the sub-100 cells/μL group, have not been done.

For the clinician, then, the practical implication is modest but real: a low count is a reason to think about bacteria, not a reason to act on them, and ICS decisions continue to rest on exacerbation history, prior infection and guideline thresholds rather than on any single laboratory value. For the researcher, the widest gaps lie in patients with counts below 100 cells/μL and in populations with a high tuberculosis burden, both of which remain little studied, and in the absence of any prospective test of whether this paradox changes outcomes.

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REFERENCES

1. Singh D, Agusti A, Martinez FJ, Papi A, Pavord ID, Wedzicha JA, et al. Blood eosinophils and chronic obstructive pulmonary disease: a Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 review. Am J Respir Crit Care Med. 2022;206(1):17-24. doi:10.1164/rccm.202201-0209PP
2. Miravitlles M, Calle M, Molina J, Almagro P, Gomez JT, Trigueros JA, et al. Update 2025 of the Spanish COPD guidelines (GesEPOC): pharmacological treatment of stable COPD. Arch Bronconeumol. 2025;61(12):766-82. doi:10.1016/j.arbres.2025.10.008
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2026 report [Internet]. GOLD; 2025 [cited 2026 Oct 27]. Available from: https://goldcopd.org
4. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med. 2018;6(2):117-26. doi:10.1016/S2213-2600(18)30006-7
5. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet. 2018;391(10125):1076-84. doi:10.1016/S0140-6736(18)30206-X
6. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease

(TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet. 2017;389(10082):1919-29. doi:10.1016/S0140-6736(17)30188-5
7. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378(18):1671-80. doi:10.1056/NEJMoa1713901
8. Lea S, Higham A, Beech A, Singh D. How inhaled corticosteroids target inflammation in COPD. Eur Respir Rev. 2023;32(170):230084. doi:10.1183/16000617.0084-2023
9. Martinez-Garcia MA, Faner R, Oscullo G, de la Rosa D, Soler-Cataluna JJ, Ballester M, et al. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease: a network analysis. Am J Respir Crit Care Med. 2020;201(9):1078-85. doi:10.1164/rccm.201908-1550OC
10. Leitao Filho FS, Takiguchi H, Akata K, Ra SW, Moon JY, Kim HK, et al. Effects of inhaled corticosteroid/long-acting beta2-agonist combination on the airway microbiome of patients with chronic obstructive pulmonary disease: a randomized controlled clinical trial (DISARM). Am J Respir Crit Care Med. 2021;204(10):1143-52. doi:10.1164/rccm.202102-0289OC
11. Song Z, Meng Y, Fricker M, Li X, Tian H, Tan Y, et al. The role of gut-lung axis in COPD: pathogenesis, immune response, and prospective treatment. Heliyon. 2024;10(9):e30612. doi:10.1016/j.heliyon.2024.e30612
12. Dicker AJ, Huang JTJ, Lonergan M, Keir HR, Fong CJ, Tan B, et al. The sputum microbiome, airway inflammation, and mortality in chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2021;147(1):158-67. doi:10.1016/j.jaci.2020.02.040
13. Sulaiman I, Wu BG, Chung M, Isaacs B, Tsay JJ, Holden D, et al. Lower airway dysbiosis augments lung inflammatory injury in mild-to-moderate chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2023;208(10):1101-14. doi:10.1164/rccm.202210-1865OC
14. Opron K, Begley LA, Erb-Downward JR, Freeman C, Madapoosi S, Alexis NE, et al. Loss of airway phylogenetic diversity is associated with clinical and pathobiological markers of disease development in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2024;210(2):186-200. doi:10.1164/rccm.202308-1370OC
15. Kayongo A, Robertson NM, Siddharthan T, Ntayi ML, Ndawula JC, Sande OJ, et al. Airway microbiome-immune crosstalk in chronic obstructive pulmonary disease. Front Immunol. 2022;13:1085551. doi:10.3389/fimmu.2022.1085551
16. Wang Z, Bafadhel M, Haldar K, Spivak A, Mayhew D, Miller BE, et al. Lung microbiome dynamics in COPD exacerbations. Eur Respir J. 2016;47(4):1082-92. doi:10.1183/13993003.01406-2015
17. Wang Z, Locantore N, Haldar K, Ramsheh MY, Beech AS, Ma W, et al. Inflammatory endotype-associated airway microbiome in chronic obstructive pulmonary disease clinical stability and exacerbations: a multicohort longitudinal analysis. Am J Respir Crit Care Med. 2021;203(12):1488-502. doi:10.1164/rccm.202009-3448OC
18. Beech AS, Lea S, Kolsum U, Wang Z, Miller BE, Donaldson GC, et al. Bacteria and sputum inflammatory cell counts; a COPD cohort analysis. Respir Res. 2020;21(1):289. doi:10.1186/s12931-020-01552-4
19. Oscullo G, Gomez Olivas JD, Ingles M, Mompean S, Martinez Perez R, Suarez Cuartin G, et al. Bronchiectasis-COPD overlap syndrome: role of peripheral eosinophil count and inhaled corticosteroid treatment. J Clin Med. 2023;12(19):6417. doi:10.3390/jcm12196417
20. Higham A, Beech A, Singh D. The relevance of eosinophils in chronic obstructive pulmonary disease: inflammation, microbiome, and clinical outcomes. J Leukoc Biol. 2024;116(5):927-46. doi:10.1093/jleuko/qiae153
21. Martinez-Garcia MA, Faner R, Oscullo G, de la Rosa D, Soler-Cataluna JJ, Ballester M, et al. Chronic bronchial infection is associated with more rapid lung function decline in chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2022;19(11):1842-7. doi:10.1513/AnnalsATS.202108-974OC
22. Perotin JM, Muggeo A, Lecomte-Thenot Q, Brisebarre A, Dury S, Launois C, et al. High blood eosinophil count at stable state is not associated with airway microbiota distinct profile in COPD. Int J Chron Obstruct Pulmon Dis. 2024;19:765-71. doi:10.2147/COPD.S453526

23. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. Lancet Respir Med. 2016;4(9):731-41. doi:10.1016/S2213-2600(16)30148-5
24. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet. 2016;387(10030):1817-26. doi:10.1016/S0140-6736(16)30069-1
25. Crim C, Calverley PMA, Anderson JA, Holmes AP, Kilbride S, Martinez FJ, et al. Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: the SUMMIT trial. Respir Med. 2017;131:27-34. doi:10.1016/j.rmed.2017.07.060
26. Castellana G, Castellana M, Castellana C, Castellana G, Resta E, Carone M, et al. Inhaled corticosteroids and risk of tuberculosis in patients with obstructive lung diseases: a systematic review and meta-analysis of non-randomized studies. Int J Chron Obstruct Pulmon Dis. 2019;14:2219-27. doi:10.2147/COPD.S209273
27. Yoon EC, Lee H, Yoon HY. Inhaled corticosteroids and the risk of nontuberculous mycobacterial infection in chronic airway disease: a nationwide population-based study. Tuberc Respir Dis (Seoul). 2024;87(4):473-82. doi:10.4046/trd.2024.0038
28. Yatera K, Wang Z, Shibata Y, Ishikawa N, Homma T, Fukushima K, et al. Sputum microbiome, potentially pathogenic organisms, and clinical outcomes in Japanese patients with COPD and moderate airflow limitation: the prospective AERIS-J study. Int J Chron Obstruct Pulmon Dis. 2025;20:1477-92. doi:10.2147/COPD.S481406
29. Chen K, Pleasants KA, Pleasants RA, Beiko T, Washburn RG, Yu Z, et al. Procalcitonin for antibiotic prescription in chronic obstructive pulmonary disease exacerbations: systematic review, meta-analysis, and clinical perspective. Pulm Ther. 2020;6(2):201-14. doi:10.1007/s41030-020-00123-8
30. Sheng W, Huang L, Gu X, Zhang H, Wang Y, Cao B. Procalcitonin-guided use of antibiotic in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized clinical trial. Clin Microbiol Infect. 2025;31(5):785-92. doi:10.1016/j.cmi.2024.12.003
31. Rowe SM, Jones I, Dransfield MT, Haque N, Gleason S, Hayes KA, et al. Efficacy and safety of the CFTR potentiator icenticaftor (QBW251) in COPD: results from a phase 2 randomized trial. Int J Chron Obstruct Pulmon Dis. 2020;15:2399-409. doi:10.2147/COPD.S257474