Blood Eosinophils and Chronic Obstructive Pulmonary Disease

A Global Initiative for Chronic Obstructive Lung Disease Science Committee 2022 Review

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The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published its first report for the diagnosis and management of chronic obstructive pulmonary disease (COPD) in 2001 (1). Since then, GOLD has updated it yearly (2), the last time in 2022 (www.goldcopd.org). To do so, GOLD critically evaluates the new evidence since the previous publication and decides whether it merits (or not) inclusion in the most recent update. GOLD publishes specific recommendations and, sometimes, the main arguments behind them, but it often lacks space for a detailed discussion regarding the pros and cons behind each recommendation. To address this limitation, the Scientific Committee of GOLD decided to publish, separately from the main annual update, a series of papers that review and discuss topics of particular current interest for clinical practice.

The GOLD 2019 report recommended using blood eosinophil counts (BEC) as part of a precision medicine strategy to identify the most suitable patients for inhaled corticosteroids (ICS) treatment (3). Recent publications have provided further evidence and insights concerning BEC in COPD. Here, we discuss the role of BEC as a COPD biomarker, focusing on new advances and summarizing the associated changes in the GOLD 2022 report (shown in Table 1).

A Brief Overview of Eosinophil Biology

Eosinophils originate from bone marrow stem cells in response to stimulation by granulocyte–monocyte colony-stimulating factor, IL-3, and IL-5 (4). The subsequent proliferation, activation, tissue infiltration, and survival of eosinophils are controlled by type-2 (T2) inflammation mediators, such as IL-4, IL-5, IL-13, and eotaxins. Eosinophil degranulation releases major basic proteins, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin, which provide host defense against parasitic infection (5). These proteins also promote bacterial and viral clearance, although the extent of these roles in humans, as opposed to animal models, is unclear (4, 5). Eosinophil-derived granule proteins can cause tissue injury and remodeling, whereas eosinophil peroxidase drives changes in the physicochemical properties of mucus that underlie airway mucus plugging (4, 6). There is also evidence that eosinophil subsets exist, with tissue-resident cells having a predominantly homeostatic role, whereas inflammatory eosinophils are recruited into the lungs (7). Asthma and systemic hypereosinophilic diseases are examples in which increased systemic and lung eosinophil numbers, coupled with activation, contribute to disease pathophysiology (4).

BEC as a Predictor of ICS Benefit

COPD is a heterogeneous condition, exemplified by the between-individual variation in the nature and severity of airway inflammation (3, 8–10). The use of antiinflammatory treatments, therefore, requires a selective approach based on clinical characteristics (phenotyping) and biological information (endotyping) to target therapies to subgroups of individuals who

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Table 1. Global Initiative for Chronic Obstructive Lung Disease 2022 Report: Key Evidence and Recommendations for Blood Eosinophil Counts in Chronic Obstructive Pulmonary Disease

Prediction of ICS benefits
The use of BEC to predict ICS effects should be combined with exacerbation risk (using exacerbation history).
The relationship between BEC and ICS effects is continuous; no/small effects are observed at lower BEC, with increasing effects at higher BEC.
Less than 100 cells/μl and ⩾300 cells/μl are estimates, not precise cutoff values, to identify individuals with the lowest and greatest (respectively) likelihood of ICS benefit.
T2 inflammation
Higher BEC are associated with increased lung eosinophil numbers and higher concentrations of T2 inflammation markers in the airways.
The differences in T2 inflammation can explain the differential ICS response according to BEC.
COPD vs. control subjects
A subset of patients with COPD has BEC above those found in control subjects.
Microbiome
Lower BEC are associated with a greater presence of proteobacteria, notably *Haemophilus*, and increased bacterial infections and pneumonia.
Future risk of exacerbations/disease progression
In younger individuals without COPD, higher BEC are associated with an increased risk of FEV_1 decline and the development of COPD.
BEC cannot be used as a standalone biomarker of future risk without considering exacerbation risk and ICS use.

Definition of abbreviations: BEC = blood eosinophil counts; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; T2 = type-2.

are most likely to derive benefit (3, 9, 11). ICS are antiinflammatory drugs used in combination with one or two long-acting bronchodilators (LABDs) for the treatment of COPD. Randomized control trials (RCTs) have shown that ICS reduce exacerbation rates, improve quality of life, and prevent mortality when targeted to patients with COPD with a history of exacerbations (3, 12, 13). Prespecified and *post hoc* analyses of these RCTs have shown that higher BEC, used as a surrogate for lung eosinophil counts (14), at the study start are associated with greater clinical benefits, notably exacerbation prevention, from ICS treatment (3, 14–17). The relationship between BEC and ICS benefits has been described as continuous, as these analyses have demonstrated treatment effects at above approximately∼100 cells/μl with incremental increases in the magnitude of effect at higher BEC (3, 14). Importantly, there is no clear evidence that ICS treatment reduces BEC, so BEC retain their predictive value independent of ICS treatment. Accordingly, in 2019, GOLD recommended the use of BEC in clinical practice in patients with COPD with an exacerbation history despite the appropriate use of LABDs to identify the most suitable patients for ICS treatment (3). The BEC thresholds of less than 100 cells/μl and 300 or more cells/μl have been proposed, identifying individuals with the lowest and greatest likelihood (respectively) of benefit from ICS treatment when administered on top of LABD. These are estimated, not strict, thresholds. Patients with low BEC appear to be at increased risk of pneumonia (18, 19) (discussed in depth later), and there is also a small increase in pneumonia risk with ICS use in patients with COPD (12, 13, 15).

RCTs of inhaled triple therapies have been analyzed according to whether patients had one or two or more exacerbations in the previous year (20, 21). A history of two or more exacerbations was associated with more exacerbations during the study than one previous exacerbation. The benefit of ICS on exacerbation prevention was greater in individuals with more events (i.e., those with a history of two or more exacerbations), but there was still a benefit in patients with one previous exacerbation, and BEC were able to predict ICS benefits regardless of exacerbation history.

In conclusion, the GOLD 2019 report recommended the use of clinical phenotyping (exacerbation history) combined with endotyping (using BEC as a biomarker) to enable ICS to be used with more precision, selecting individuals with a greater benefit (reduction in exacerbations) versus risk profile (pneumonia occurrence), hence increasing the net benefit potential of ICS (3). RCT results published since 2019 remain supportive of BEC as a predictive biomarker of ICS effects in patients with COPD with increased exacerbation risk (15).

Variability of BEC

The intraclass correlation coefficient for repeated BEC measurements performed on different days in patients with COPD has ranged from 0.64 to 0.89, indicating good to excellent reproducibility (14). It has been commented that similar intraclass correlation coefficient values have been reported for cholesterol and glycated hemoglobin, which are routinely used biomarkers in clinical practice (3, 14). BEC show diurnal variation in healthy subjects and patients with asthma and COPD, peaking in the early morning and thought to be related to circadian variation in cortisol secretion (22, 23). The median reduction in BEC at 12.00 compared with 8.00 in patients with COPD was reported to be 36% (23).

GOLD has suggested BEC thresholds to help direct ICS treatment (3). Movement across a threshold after repeated measurement is more likely for BEC that are closer to the threshold (24). This is one reason why GOLD states that these are not strict thresholds, and consequently, small within- or between-day variations should not result in a change in clinical management. In support, it has been reported that the predictive ability of BEC, with regard to ICS benefits observed in a triple therapy RCT, were similar regardless of whether the BEC at screening or randomization was used or the average of both (25).

BEC in Patients with COPD Versus Control Subjects

A study in individuals more than 40 years old showed that, on average, eosinophil counts were higher in patients with COPD ($n = 209$) than in control subjects ($n = 127$) (26). Although there was considerable overlap in the counts between the groups, some patients with COPD had higher counts than the control subjects. A recent cohort study has also shown that BEC are higher in patients with COPD ($n = 326$) versus control subjects ($n = 399$) (27). In contrast, other studies have not shown differences between patients with COPD and control subjects (28), as the CanCOLD (Canadian Cohort Obstructive Lung Disease) study showed a similar distribution of BEC between the non-COPD ($n = 573$) and COPD ($n = 547$) participants (29), whereas the CHAIN (COPD History Assessment in Spain) cohort also showed a similar BEC distribution between non-COPD ($n = 121$) and COPD ($n = 769$) participants (30).

A large general population study in Austria ($n = 11,042$) using multivariate logistic regression showed that a higher BEC (>210 cells/μl; the 75th percentile) was more likely in current smokers (odds ratio, 1.72; 95% confidence interval [CI], 1.52–1.96) and COPD (odds ratio, 1.56; 95% CI, 1.20–2.03), but the range in patients with COPD was not specified (31). In Japanese patients with COPD ($n = 848$), the median (interquartile range) BEC was 170 cells/μl (100–280 cells/μl) with a similar distribution to that in non-Japanese patients with COPD ($n = 5,397$), but the counts were not compared with healthy control subjects (32). Another large general population study, conducted in Japan (approximately 10,000 participants), showed a similar BEC distribution in a healthy population to that seen in the European study, but BEC in patients with COPD were not reported (33).

A meta-analysis reported that the median BEC was higher in patients with COPD compared with control subjects, although the 95% CIs overlapped (34). There was high heterogeneity between studies, likely because of different characteristics of populations, particularly control subjects in which comorbid conditions that increase BEC (e.g., current smoking, allergies, and obesity [31]) may not have been fully accounted for.

In conclusion, although the evidence is not consistent across all publications, there are three studies, including a very large population study, showing that, on average, BEC are higher in patients with COPD, with a subgroup of patients with COPD showing higher counts than seen in control subjects (26, 27, 31). These observations suggest upregulation of mechanisms that increase eosinophil production from the bone marrow (i.e., the action of granulocyte–monocyte colony-stimulating factor, IL-3, and IL-5 [4]) or eosinophil survival in some patients with COPD. The lack of consistency across studies may reflect sample size and/or the influence of comorbidities on BEC (31).

BEC: Association with Future Risk or Disease Progression

FEV_1 Decline

In healthy individuals who did not have asthma in the Dunedin Multidisciplinary Health and Development Study ($n = 971$), higher BEC were associated with faster FEV_1 decline between the ages of 21 and 38 years (35). The relationship persisted after adjusting for smoking. Another study retrospectively analyzed private healthcare screening records ($n > 359,000$) of younger adults without a history of asthma or airflow obstruction (mean age, 36 years; median follow-up, 5.6 years) (36). The development of airflow obstruction was associated with higher BEC at baseline, which was also observed in the smoker subgroup. In addition, there was an association between higher BEC and the development of physician-diagnosed COPD plus spirometric confirmation of airflow obstruction, defined as $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$. A limitation of this study is that postbronchodilator spirometry was not performed. In the CANCOLD study ($n = 1,120$; mean age, 65 years), using a multivariate regression model which accounted for baseline factors including FEV_1, exacerbation history, and ICS use, individuals with BEC $\geq$300 cells/μl had more rapid FEV_1 decline than those with $<$150 cells/μl (mean difference, 34.3 ml/year) (29). The same pattern was apparent in the COPD subgroup ($n = 466$). Overall, these data from large cohort studies show that higher BEC are associated with more rapid FEV_1 decline both in younger adults without airflow obstruction and patients with COPD and, in some individuals, this leads to the development of COPD.

Data from United Kingdom electronic medical records from patients with COPD with FEV_1 50–90% predicted ($n = 12,178$) showed greater FEV_1 decline in patients with more exacerbations over more than 3 years of follow-up (37). There was an interaction between exacerbation frequency and BEC, with a more rapid loss of lung function in patients with 2 or more exacerbations per year and BEC $\geq$ 350 cells/μl, which was reduced by ICS use. However, in patients without exacerbations, the rate of FEV_1 decline was approximately 10 ml per year less in patients with BEC $\geq$ 350 cells/μl compared with those with lower BEC. This study confirms the importance of exacerbations as a determinant of FEV_1 decline (38) and demonstrates complex relationships between BEC and FEV_1 decline dependent on both exacerbation frequency and ICS use. An analysis of more than 26,000 patients with COPD from the same database source showed that new ICS use versus no ICS use was associated with reduced FEV_1 decline in subjects with BEC $>$ 150/μl (39), but exacerbations were not analyzed. A *post hoc* analysis of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study also showed that in patients with BEC $\geq$ 2%, FEV_1 decline was reduced by ICS treatment (40). The Hokkaido COPD cohort, with a smaller sample size ($n = 279$) and low ICS use ($<$15%), reported that mean BEC were lower in the rapid decliners compared with the slow decliners or sustainers (41). Again, exacerbations were not reported in this study.

In conclusion, in younger individuals without COPD, there is evidence of an association between higher BEC and both faster FEV_1 decline and the development of airflow obstruction (35, 36). These observations mechanistically implicate eosinophils and/or other associated components of T2 inflammation in the development of COPD, at least in some patients. In patients with confirmed COPD, the association between higher BEC and FEV_1 decline is complex, and findings from cohort studies have been inconsistent, being influenced by disease heterogeneity, including prior exacerbation frequency and use of ICS (37–39). These complexities mean that using BEC alone in patients with COPD to predict lung function decline is a simplistic approach that is unlikely to be of clinical utility. Nevertheless, FEV_1 decline appears to be greater in individuals with more exacerbations (37, 38), and ICS may

reduce the rate of decline in individuals with greater exacerbation risk plus higher BEC (37). These observational data, following patients with COPD for 3 or more years, support the results of multiple RCTs conducted over 1 year; both demonstrate a relationship between BEC and ICS benefits in patients with COPD with a history of exacerbations (14–16, 42).

Exacerbation Risk

Some cohort studies have reported an association between BEC and exacerbation risk in patients with COPD, whereas others have found no relationship (30, 43–49). These contradictory findings generally reflect differences in baseline exacerbation history (which is the strongest predictor of exacerbation risk [50]) and ICS use, which RCTs have shown weaken the relationship between exacerbation risk and BEC (14, 16, 17, 42). Cohort studies have generally not adjusted for these factors. Analysis of two cohorts with prospective follow up data ($n = 1{,}113$ and $n = 1{,}895$) reported that BEC $\geq$ 300 cells/μl were associated with increased exacerbation frequency; this association was driven by the subgroup of individuals with 2 or more exacerbations in the year before study start, with incident risk ratios of 1.96 and 1.4 for individuals with BEC $\geq$ 300 cells/μl versus $<$300 cells/μl in this subgroup (51). The relationships between BEC and exacerbation risk remained after adjusting for ICS use.

Analyses of RCTs investigating ICS-containing combination treatments in patients with COPD with a history of exacerbations have shown that higher baseline BEC are associated with a higher rate of exacerbations over 12 months in patients not treated with ICS (15–17, 42). In contrast, a pooled analysis of 11 RCTs investigating LABD involving patients with and without a history of exacerbations found no relationship between BEC and exacerbation rates in patients not taking ICS (who also had lower exacerbation rates) (52). Exacerbation rates in patients taking ICS with were slightly higher (9%) in patients with BEC $>$300 cells/μl compared with those with counts $\leq$ 150 cells/μl (52).

In conclusion, exacerbation history remains the best predictor of future exacerbation risk (50, 51). The potential usefulness of BEC as a predictor of future exacerbation risk is restricted to patients with a history of exacerbations, and BEC have been consistently associated with exacerbation risk in the non-ICS treatment arms of RCTs involving this clinical phenotype (15–17, 42). However, in cohort studies, this relationship is less consistent, being modified by ICS use and influenced by the inclusion of individuals with low exacerbation risk (30, 43–49, 51). Consequently, BEC are not a useful standalone biomarker of exacerbation risk in clinical practice.

Mortality

In the CHAIN and BODE (body mass index, airflow obstruction, dyspnea, exercise performance cohorts), all-cause mortality over 20 years was lower in patients with COPD with high BEC compared with those with values $<$300 cells/μl (15.8% vs. 33.7%; $P = 0.026$) after adjusting for age, sex, body mass index, lung function, and Charlson index (30). Over half the patients were taking ICS, but the analysis was not adjusted for this. In a French cohort, there was no relationship between BEC and 3-year survival, with over 85% of patients taking ICS (46). The ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) RCT, conducted in patients at high exacerbation risk, showed that the benefit of ICS (as part of triple combination treatment) on mortality was greater at higher BEC (53). This mortality benefit due to ICS was accompanied by exacerbation prevention at higher BEC (15).

In conclusion, BEC alone are not a reliable predictor of mortality, as the risk is modified by ICS use. However, in the high exacerbation risk phenotype, RCT evidence supports higher BEC as a biomarker of increased mortality risk in individuals not using ICS (53).

BEC and T2 Inflammation

The consistent relationship between BEC and ICS effects on exacerbation rates in COPD RCTs indicates that BEC reflect differential profiles of pulmonary inflammation within a heterogeneous condition (14, 16, 17, 54). Significant associations have been reported between BEC and pulmonary eosinophil counts (from sputum or lung tissue), with the strength of the relationship ranging from 0.18 to 0.7 (49, 55–60). Although these studies confirm that BEC reflect pulmonary eosinophil numbers, the association has been weak in some studies. The reasons for a weak association include the inherent variability of lung sampling (e.g., between-day variation in sputum eosinophil counts [10]) and sometimes a lack of methodological precision in eosinophil counts (e.g., using only one significant figure for BEC) (49). Furthermore, the distribution of eosinophils in lung tissue is patchy (61), which may explain the lack of association between blood and tissue eosinophils in one study (62) in contrast to the positive relationship reported in other studies (55, 63, 64).

Studies using bronchoscopy, induced sputum, and lung surgical tissue samples have demonstrated a T2 inflammation profile in patients with higher BEC. Kolsum and colleagues obtained bronchoscopy and sputum samples from 41 patients with COPD with higher ($>$250 cells/μl) or lower ($<$150 cells/μl) BEC (64) and no previous asthma diagnosis or skin testing evidence of atopy. The higher BEC group had increased eosinophil counts in sputum, BAL, and bronchial mucosal tissue, plus increased protein levels of mediators involved in eosinophil activation and chemotaxis (IL-5 and C-C motif chemokine ligand 24 [CCL24]). The higher BEC group also exhibited increased reticular basement membrane thickening. A subsequent analysis of this study focused on the gene expression of six T2 markers increased in patients with asthma (65). Four genes, namely chloride channel accessory 1 (CLCA1), CCL26, IL-13, and cystatin SN (CST1), had increased expression in both sputum cells and bronchial brushings in the higher BEC COPD group, with these results validated in sputum samples from a different cohort ($n = 33$). Bronchial epithelial brushings from EvA (Emphysema versus Airway disease) study ($n = 283$) also showed differential gene expression in bronchial brushings from patients with COPD with higher BEC, including CLCA1, CCL26, and CST1 (66). An asthma cohort analyzed by the authors for comparison showed far more differentially expressed genes associated with BEC, suggesting a restricted T2 signature in COPD compared with asthma. Sputum cells obtained at the baseline visit of an RCT showed a differential gene expression profile in samples with eosinophil counts $\geq$3% versus $<$3%, including known T2 markers (67). Jogdand and colleagues reported that eosinophil numbers in the conducting airways and lung parenchyma were associated with

more severe COPD and tissue basophil counts (61).

In conclusion, higher BEC in patients with COPD are associated with increased numbers of eosinophils and levels of markers of T2 inflammation in the lungs (64–66). This differential inflammation profile could explain the association between BEC and ICS responses, as T2 inflammation can respond well to corticosteroid treatment (68, 69). RCTs of biological treatments targeting IL-5 or the IL-5 receptor, thereby reducing BEC, have failed to demonstrate efficacy on exacerbation rates (the primary endpoint) in COPD populations enriched for increased exacerbation risk and higher BEC (70, 71). A contributor to these negative outcomes is that higher BEC appear to mark a wider T2 inflammation profile (61, 64–66), and selective depletion of eosinophil numbers will not modulate other T2 components. BEC could be used as a biomarker to identify patients with COPD suitable for clinical trials of novel therapeutics targeting T2 pathways (14).

BEC and Microbiome

Sputum samples obtained during the stable state from 510 patients with COPD were analyzed for cell counts and microbiome characteristics (by 16S ribosomal RNA sequencing) (10). Cross-sectional analysis showed that neutrophilic inflammation was associated with heterogeneous microbiome patterns, including a subset with a Haemophilus-dominant microbiome. In contrast, eosinophilic inflammation was associated with several nondominant genera but not Haemophilus. Longitudinal analysis showed that eosinophilic samples that became noneosinophilic over time also did not display a Haemophilus-dominant microbiome. Similarly, studies in patients with COPD using quantitative PCR quantification of bacterial species have shown that Haemophilus influenza presence is associated with higher sputum neutrophil counts and lower sputum eosinophil counts (72–74). Interestingly, bronchoscopy samples from patients with COPD with lower (vs. higher) BEC showed decreased immunoglobulin subtype amounts and reduced opsonization of nontypeable Haemophilus influenza; this provides a possible explanation for higher sputum Haemophilus influenza levels in patients with lower eosinophil counts (75).

Dicker and colleagues showed that higher BEC were associated with lower proteobacteria abundance (which includes the Haemophilus genera) and greater abundance of the Firmicutes phyla in a cohort of 296 patients with COPD (76). Furthermore, there was an increase in Haemophilus abundance for patients with BEC $\leq$100 cells/μl compared to $>$100 cells/μl. Subgroup analysis showed that the profile of inflammatory proteins in sputum was different in samples with proteobacteria dominance, favoring mediators of neutrophilic inflammation when compared to Firmicutes-dominant samples. Overall, these cohort studies have highlighted that lower eosinophil counts (in sputum and blood) are associated with a different microbiome profile, characterized by increased proteobacteria.

Martinez-Garcia and colleagues reported that BEC $<$ 100 cells/μl were associated with an increased incidence of chronic bacterial infection (CBI) and pneumonia episodes in 201 patients with COPD (median follow-up, 7 years) (19). A multivariate regression model showed that age, FEV_1, CBI, and BEC $<$ 100 cells/μl were all independently associated with greater pneumonia risk. Higher BEC thresholds ($<$150 cells/μl and $<$300 cells/μl) were not significantly associated with increased pneumonia risk. ICS use was not associated with pneumonia risk in the overall population, although ICS further increased the risk of pneumonia (hazard ratio, 2.9) in those with CBI and less than 100 eosinophils/μl. A pooled analysis of 10 randomized control trials of ICS-containing combination treatments in patients with COPD showed that the risk of pneumonia was higher in patients at baseline BEC $<$2% versus $\geq$2% (hazard ratio, 1.31; 95% CI, 1.06–1.62) (18). A potential explanation for these pneumonia findings comes from a small COPD RCT ($n = 60$) that showed ICS-containing combination treatment over one year increased sputum bacterial load, in contrast to no change without ICS; this increase was present in those with lower BEC only (77).

In conclusion, recent studies have consistently shown that lower sputum and blood eosinophil counts are associated with an increased presence of proteobacteria phylum/Haemophilus genera (10, 72–74, 76). Lower BEC also appear to be associated with an increased risk of recurrent bacterial infections and pneumonia, and these risks seem to be increased by ICS use in patients with lower BEC (18, 19, 77). Overall, these findings regarding microbiome and pneumonia risk provide additional reasons not to use ICS in patients with COPD with lower BEC.

Discussion

The GOLD 2019 report first introduced BEC as a biomarker to help make pharmacological treatment decisions concerning ICS use in patients with COPD with a history of exacerbations (3). The GOLD 2022 report now adds various additional evidence concerning BEC (key points shown in Table 1), including the connections between BEC, T2 inflammation (61, 64–66), and lung microbiome (10, 72–74, 76), which identify COPD subgroups with increased ICS response (higher BEC) or increased risk of bacterial infection (lower BEC); summarized in Figure 1. This evidence supports an integrated evaluation of clinical history (notably exacerbation history), BEC, and sputum microbiology to provide a personalized management approach with regard to when ICS should be used on top of LABD and the management of airway infection.

Accumulating evidence indicates an association between lower BEC and the incidence of both CBI and pneumonia events (18, 19), coupled with a differential microbiome profile (greater abundance of Haemophilus influenza) (10, 72–74, 76). On the basis of this evidence, lower BEC ($<$100 cells/μl) could be used as a biomarker in combination with clinical history to help identify patients who require careful monitoring for bacterial colonization. Furthermore, in these individuals, the absence of T2 inflammation coupled with the increased risk of bacterial infection argues against the use of ICS. The importance of bacterial colonization was demonstrated in an observational COPD cohort in which exacerbation risk was greatest in individuals with Haemophilus influenza colonization and exposure to rhinovirus infection (78), indicating an interplay between pathogens leading to worse clinical outcomes. Further studies should elucidate the mechanisms responsible for the association between T2 inflammation and the microbiome, as this may help identify novel therapeutic interventions.

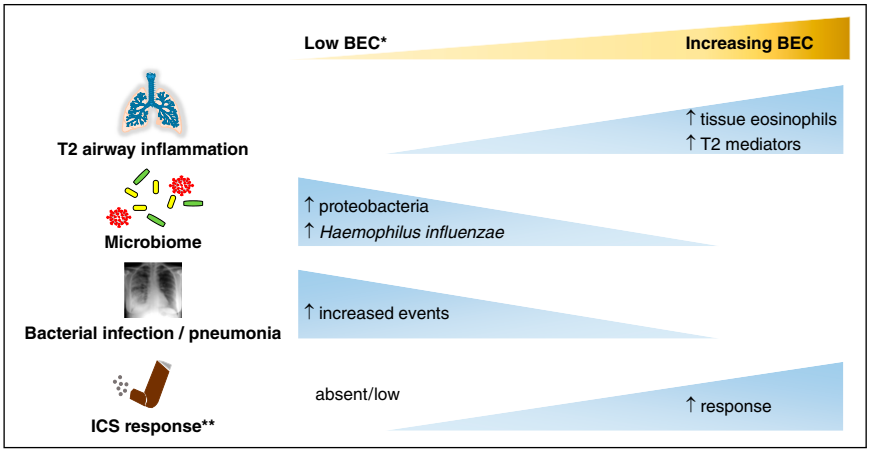

Figure 1. The relationships between blood eosinophil counts (BEC) and type-2 (T2) inflammation, microbiome, bacterial infection/pneumonia episodes, and ICS response (exacerbation prevention). ICS = inhaled corticosteroid. *<100 cells/μL. **In patients with chronic obstructive pulmonary disease who have increased exacerbation risk.

Patients with COPD with higher BEC have more T2 inflammation (61, 64–66), which can explain a differential response to ICS. It is important to note that RCTs have demonstrated a benefit for ICS (as part of combination treatments) only in patients with COPD with an exacerbation history in the previous year (3, 14). There is currently no evidence supporting ICS intervention in patients with COPD with higher BEC but without a history of exacerbations, although this is an evidence gap worth considering. Furthermore, the association between higher BEC and FEV_1 decline in younger adults (36) provides a rationale for studying the effects of ICS on disease progression/lung function decline in younger patients with COPD with higher BEC (79).

BEC are not a standalone biomarker of future risk (of FEV_1 decline, exacerbations, and mortality) in patients with COPD because of the complex relationship with exacerbation risk and confounding owing to ICS use (37). However, in younger individuals, higher BEC may serve as a biomarker to help identify those at increased risk of developing COPD (36), and further evidence is needed to evaluate the utility of BEC in this context.

RCTs have shown that in patients with COPD with a history of exacerbations, higher BEC identify a subgroup with increased exacerbation risk that can be therapeutically modified by ICS (15–17). On the other hand, we also point out a subgroup with lower BEC (<100 cells/μl) with a different microbiome profile and increased risk of chronic bacterial infection (19, 76). These findings might suggest that BEC predict a "U-shaped" future risk curve, albeit one that is influenced by other factors, including exacerbation history and ICS use.

Conclusions

The GOLD 2022 report incorporates new evidence regarding BEC, notably the relationships between T2 inflammation (64–66) and the microbiome (10, 72–74, 76). These findings further our understanding of COPD subtypes, facilitating precision medicine strategies on the basis of clinical phenotyping combined with endotyping (9, 11). ■

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