

Biologic Management in Severe Asthma for Adults

An American College of Chest Physicians Clinical Practice Guideline



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BACKGROUND: Severe asthma affects 5% to 10% of patients with asthma but constitutes close to one-half of the medical costs related to asthma due to higher morbidity and health care utilization. Biologic agents have become a standard of care in those unresponsive to standard treatments yet the choice of biologic agent is complex due to the varying mechanisms of action, efficacies, and lack of head-to-head comparisons. Therefore, clinicians need further clinical guidance to optimize their use.

STUDY DESIGN AND METHODS: Panelists developed key clinical questions utilizing the population, intervention, comparator, and outcome (PICO) format to address choice of a biologic agent in severe asthma for adult patients aged ≥ 18 years. A comprehensive systematic search was performed using MEDLINE (via OVID), EMBASE, Web of Science, and CINAHL to identify relevant articles, which were then screened for inclusion using document evaluation tools. Each included article underwent quality assessment, data extraction, and pooled analysis to support grade level recommendation for each of the PICO questions.

RESULTS: Our systematic review and critical analysis of the literature on the 7 PICO questions related to choice of biologic agent in severe asthma patients resulted in 7 evidence-based recommendations.

INTERPRETATION: Characteristics such as quality of life impairment, baseline lung function, frequency of exacerbation, baseline oral corticosteroid use, asthma endotype, biomarkers, and comorbid conditions can impact the biologic choice. Evidence for selecting biologic agents in severe asthma is limited by the absence of comparative effectiveness trials. Additional high-quality evidence is needed to inform choice of biologic agents in these patients.

CHEST 2026; 169(2):336-348

KEY WORDS: benralizumab; biologic; dupilumab; eosinophilic asthma; fractional exhaled nitric oxide; mepolizumab; monoclonal antibody; omalizumab; reslizumab; severe asthma; severe persistent asthma; tezepelumab

ABBREVIATIONS: AQLQ = Asthma Quality of Life Questionnaire; AEC = absolute eosinophil count; CRSwNP = chronic rhinosinusitis with nasal polyposis; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; MD = mean difference; OCS = oral corticosteroid; PICO = population, intervention, comparator, and outcome; QoL = quality of life; RR = relative risk

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Summary of Recommendations

Background

Severe asthma is estimated to affect 5% to 10% of individuals with asthma although some studies report a prevalence upwards of 38% globally.^{1,2} According to the American Thoracic Society/European Respiratory Society joint guidelines, severe asthma is defined as patients who required high-dose inhaled corticosteroids (ICSs) plus a second controller, with or without systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.³ While most asthma is effectively managed with inhaled therapies, people with severe asthma may experience frequent exacerbations and requirements for oral corticosteroids (OCSs) which increase morbidity and mortality. These patients account for a disproportionate utilization of health care services and resources and often experience a number of deleterious complications related to frequent or prolonged OCS usage.²

For patients who continue to exacerbate despite escalations in standard treatments per Global Initiative for Asthma guidelines,⁴ who have been evaluated for proper adherence and inhaler technique, and who have also been appropriately evaluated and treated for other co-morbid conditions such as reflux, chronic sinusitis, vocal cord dysfunction, and dysfunctional breathing, etc, biologic agents should be considered.⁵

Clinicians have several biologic agents to consider when selecting the most appropriate therapy.² At the present time, biologics are most often considered for patients

with eosinophilic asthma.⁶ Eosinophilia is detected via clinically available biomarkers, contingent upon available health care resources. While there has yet to be a universally agreed upon definition for T2 high asthma (or eosinophilic asthma), an absolute eosinophil count (AEC) ≥ 300 cells/ μ L, fractional exhaled nitric oxide (FENO) ≥ 25 ppb, and/or sputum eosinophils $\geq 1\%$ to 3% are referred to as T2 high asthma.⁷ Asthma that is predominantly triggered by allergens is defined as allergic asthma. Patients who do not exhibit these features are considered to be T2 low. It is estimated that about 50% or more of all patients with severe asthma exhibit a T2 high endotype, whereas T2 low asthma may make up considerably less of the overall asthma population of around 10% to 30%.^{8,9} Each of the biologic agents has a slightly different mechanism of action but similarly target different cytokines or receptors involved in the T2 inflammatory pathway as shown in Figure 1⁸ and summarized in Table 1. Anti-thymic stromal lymphopoietin, an epithelial alarmin, activates multiple innate and adaptive immune responses in addition to the T2 pathway.

As there are currently no comparative effectiveness trials, and indirect meta-analyses often demonstrate discordant results, providers currently lack evidence-based guidance on biologic selection in people with severe asthma, leading to variations in practice patterns.⁶ While there is evidence-based information to initiate the most appropriate initial biologic agent, there is considerably less guidance informing how to proceed once patients do not achieve the desired clinical response.^{11,12} Choosing the most effective biologic promptly can reduce excess morbidity and untoward side effects from OCSs.

This CHEST organization guideline seeks to provide asthma providers with a framework for effectively choosing a biologic agent based on the currently available evidence.

Study Design and Methods

A multidisciplinary expert panel conducted a systematic review addressing 7 questions developed using the population, intervention, comparator, and outcome (PICO) format (e-Table S2). The population included adult patients (≥ 18 years old) with severe asthma and all recommendations issued were for this population unless stated otherwise. The panel employed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for assessing the

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DOI: <https://doi.org/10.1016/j.chest.2025.08.042>

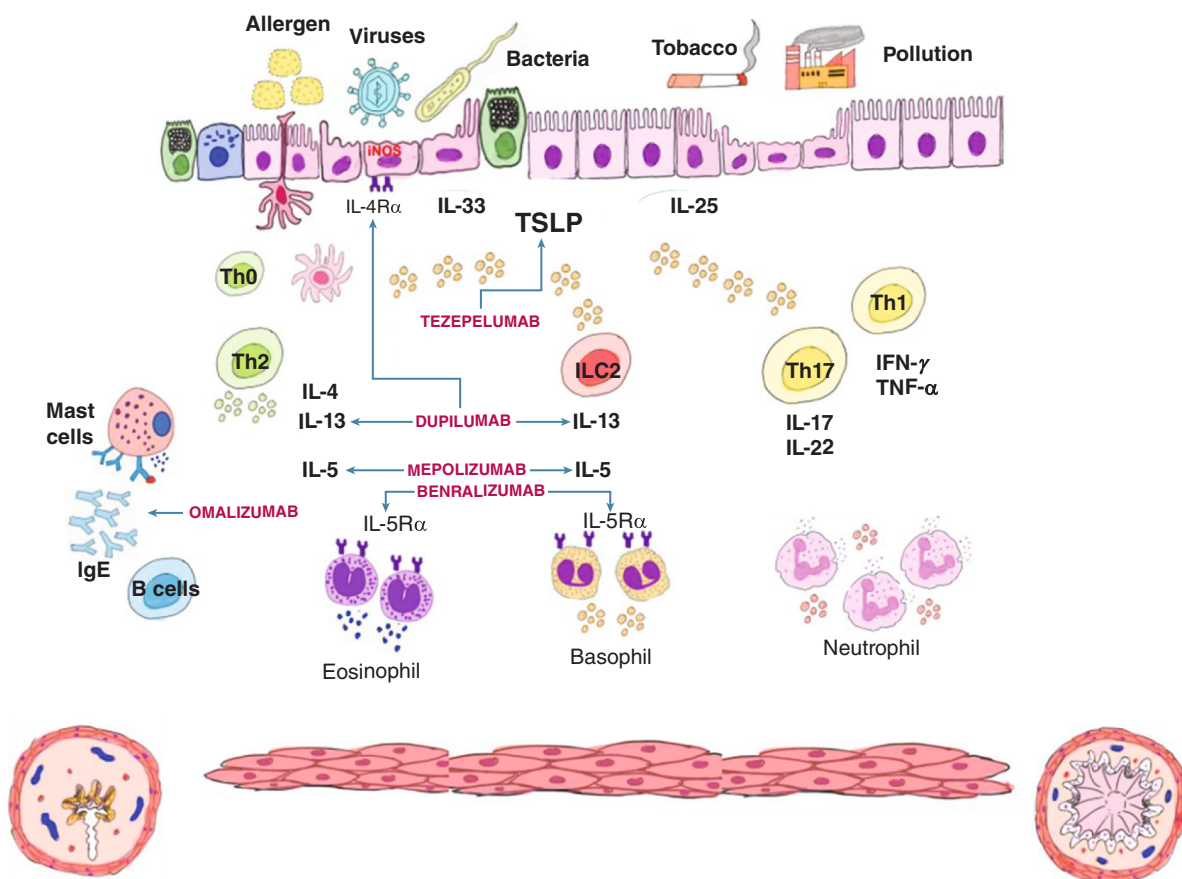


Figure 1 – Pathophysiology of asthma, biologics, and associated therapeutic targets. IFN- γ = interferon gamma; ILC2 = innate lymphoid cell 2; iNOS = inducible nitric oxide synthase; Th = T-helper; TNF- α = tumor necrosis factor- α ; TSLP = thymic stromal lymphopoietin. Adapted with permission from Sardon-Plado et al.¹⁰

certainty of evidence and formulating and grading clinical recommendations. For detailed methodology, see e-Appendix 1.

Panel Composition

The guideline panel consisted of 2 chairs (A. J. O. and F. H.), 9 additional panelists (F. A., I. A., M. P. A., M. C., A. O. C. Y., N. S., F. F. L., M. P. A., and R. R.), and one methodologist (M. J. M.), totaling 12 members. The multidisciplinary panel included pulmonologists and allergists, representing 3 countries. Panelists were selected

based on expertise in severe asthma and related subspecialties. All members were screened for potential conflicts of interest and approved by the CHEST organization's Professional Standards Committee.

Question Development and Literature Review

Seven key clinical questions were developed using the PICO format (e-Table S1). The questions were developed according to the CHEST organization guideline topic submission process (<https://www.chestnet.org/guidelines-and-topic-collections/guidelines/chest-guideline-development-and-submissions>). The 7 PICO questions were developed with a focus on areas of unmet clinical need to help clinicians streamline the selection process in an area where multiple agents are used for the same disease process and to provide some guidance on switching agents when patients lack an appropriate clinical response (Table 2). The decision was made to highlight unique differences in steroid dependent patients but also include asthmatic participants without steroid dependency. In doing so, while maintaining the format

TABLE 1] List of Biologics in Asthma

Drug Target	Drug Name(s)
Anti-IgE	Omalizumab
Anti-IL5/5R α	Mepolizumab, reslizumab, benralizumab (anti-IL5R α)
Anti-IL4R α /13	Dupilumab
Anti-TSLP	Tezepelumab

TSLP = thymic stromal lymphopoietin.

TABLE 2 | Summary of PICO Questions and Recommendations

PICO	Question	Recommendation	Strength of Recommendation	Supporting Evidence
1	Should adult patients aged ≥ 18 y with moderate to severe allergic asthma and history of ≥ 1 exacerbation per year requiring oral corticosteroids be treated with dupilumab or omalizumab?	In adult patients with moderate to severe allergic asthma and history of ≥ 1 exacerbation per year requiring oral corticosteroids, the panel suggests either omalizumab or dupilumab. A. For patients with frequent exacerbations (≥ 2 per year) or any severe exacerbation requiring hospitalization, the panel suggests dupilumab over omalizumab. B. For patients with more severe impairments in quality of life, (and < 2 exacerbations per year), the panel suggests omalizumab over dupilumab. C. For patients with a greater impairment in lung function ($FEV_1 < 70\%$ predicted), the panel suggests dupilumab over omalizumab.	Conditional	Very low certainty
2	Should adult patients with steroid dependent asthma be treated with anti-IL5/5R α or dupilumab?	In adult patients with severe asthma who are steroid dependent, the panel suggests either anti-IL5/5R α therapy or dupilumab.	Conditional	Very low certainty
3	Should adult patients with steroid dependent asthma be treated with dupilumab or tezepelumab?	In adult patients with severe asthma who are steroid dependent, the panel suggests dupilumab over tezepelumab.	Conditional	Very low certainty
4	Should adult patients with moderate to severe asthma who have not demonstrated a clinical response to omalizumab after 4-6 mo be treated with anti-IL5/5R α or dupilumab?	In adult patients with moderate to severe asthma who have not demonstrated a clinical response to omalizumab after 4-6 mo, the panel suggests either anti-IL5/5R α therapy or dupilumab.	Conditional	Very low certainty
5	Should adult patients with severe asthma who have not demonstrated a clinical response to anti-IL5/5R α after 4-6 mo be treated with dupilumab or tezepelumab?	In adult patients with severe asthma who have not demonstrated a clinical response to anti-IL5/5R α therapy after 4-6 mo, the panel suggests either dupilumab or tezepelumab. A. For patients who are steroid dependent, the panel suggests dupilumab over tezepelumab.	Conditional	Very low certainty
6	Should adult patients with severe asthma who have not demonstrated a clinical response to dupilumab after 4-6 mo be treated with anti IL5/5R α or tezepelumab?	In adult patients with severe asthma who have not demonstrated a clinical response to dupilumab after 4-6 mo, the panels suggests either anti-IL5/5R α or tezepelumab. A. For patients who are steroid dependent, the panel suggests anti-IL5/5R α .	Conditional	Very low certainty
7	Should F _{ENO} be used for guiding changes in therapy to dupilumab in adult patients with severe asthma on anti-IL5/5R who have not demonstrated a clinical response by 4-6 mo?	In adult patients with severe asthma on anti-IL5/5R α who have not demonstrated a clinical response by 4-6 mo, the panel suggests the use of post treatment F _{ENO} ≥ 25 ppb for advising changes in therapy to dupilumab.	Conditional	Very low

F_{ENO} = fractional exhaled nitric oxide.

of comparing 1 agent (intervention) to another (comparator), it was not logistically possible to include all possible intervention-comparator options because of CHEST organization recommendations on PICO question limit as well as *CHEST* journal manuscript word count limits. As a result, this guideline is not an exhaustive list of choices when prescribing biologic therapy but rather is developed to represent common clinical questions that non-asthma/biologic specialists would encounter in the real world. The panel had unanimous agreement to proceed with the questions submitted to the CHEST organization Guidelines Oversight Committee for this clinical practice guideline. A systematic literature review was conducted with the support of a medical librarian, covering MEDLINE, EMBASE, CINAHL, Web of Science, and

CENTRAL, restricted to English-language systematic reviews and randomized controlled trials. The initial search was performed in October 2022, with ongoing literature monitoring through August 2024.

Evidence Appraisal and Recommendation Process

The panel applied the GRADE approach to evaluate the certainty of evidence and formulate recommendations. Draft recommendations were discussed in virtual meetings and finalized through up to 3 rounds of modified Delphi voting conducted via SurveyMonkey. A minimum of 80% agreement in directionality and at least 75% panel participation were required for consensus. Panelists with relevant conflicts abstained from voting on specific recommendations.

Results

Additional considerations with respect to choice of biologic in the context of comorbidities, as well as panel consensus and more detail on subgroup considerations can be reviewed in the Evidence-to-Decision documents in the [Supplemental Appendix](#).

PICO 1

Question 1: Should adult patients aged ≥ 18 years with moderate to severe allergic asthma and history of ≥ 1 exacerbation per year requiring oral corticosteroids be treated with dupilumab or omalizumab?

CHEST Recommendation: In adult patients with moderate to severe allergic asthma and history of ≥ 1 exacerbation per year requiring oral corticosteroids, the panel suggests either omalizumab or dupilumab (Conditional Recommendation, Very Low Certainty of Evidence).

- A. **For patients with frequent exacerbations (≥ 2 per year) or any severe exacerbation requiring hospitalization, the panel suggests dupilumab over omalizumab (Conditional Recommendation, Very Low Certainty of Evidence).**
- B. **For patients with more severe impairments in quality of life (and < 2 exacerbations per year), the panel suggests omalizumab over dupilumab (Conditional Recommendation, Very Low Certainty of Evidence).**
- C. **For patients with a greater impairment in lung function ($FEV_1 < 70\%$ predicted), the panel suggests dupilumab over omalizumab (Conditional Recommendation, Very Low Certainty of Evidence).**

Allergic asthma makes up over one-half of all new asthma diagnoses in the second to third decades of life but represents $< 40\%$ of all new cases for individuals aged 40 years and older.¹³ Despite standard of care therapy with inhaled, oral, and intranasal therapies, and after undergoing appropriate avoidance measures, some patients continue to experience recurrent exacerbations.

Both omalizumab and dupilumab lead to a significant reduction in asthma exacerbations (42% vs 44%) respectively ([e-Table S3](#)). Omalizumab showed a greater improvement in quality of life (QoL) scores as compared to dupilumab (Asthma Quality of Life Questionnaire [AQLQ], 0.53 [95% CI, 0.29-0.77] vs 0.28 [95% CI, 0.18-0.37], respectively) ([e-Table S3](#)) resulting in the conditional recommendation to consider omalizumab in patients who are not frequent exacerbators but have more negative impacts in their QoL. QoL was determined by using the AQLQ and includes 32 questions used to assess physical, emotional, occupational, and social quality of adults.¹⁴ Neither agent resulted in a statistically significant improvement in asthma control as defined by the asthma control test or asthma control questionnaire ([e-Table S3](#)).

Dupilumab resulted in a greater improvement in FEV_1 compared to omalizumab (140 mL vs 50 mL) respectively ([e-Table S3](#)). While both agents demonstrated a reduction in baseline OCS dose, it is noteworthy to mention that there were only 2 randomized controlled trials that assessed the steroid sparing ability of each of these agents, which contributes to the low certainty of evidence. The panel made a conditional recommendation to consider dupilumab over omalizumab in patients with more frequent or severe

exacerbations despite the studies having similar baseline exacerbations because the study population in the omalizumab study was deemed less severe due to fewer controller agents and a higher baseline FEV₁. Adverse event rates were slightly higher with dupilumab as compared to omalizumab (relative risk [RR], 1.05 vs 0.81 respectively), which may also be explained by differences in severity of illness across studies (e-Table S3).

PICO 2

Question 2: Should adult patients with steroid dependent asthma be treated with anti-IL5/5R α or dupilumab?

CHEST Recommendation: In adult patients with severe asthma who are steroid dependent, the panel suggests either anti-IL5/5R α therapy or dupilumab (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: In cases where pre-OCS dependency AEC is > 1,500 cells/ μ L the clinician may consider use of anti-IL5/5R α due to the potential risk of hypereosinophilia with dupilumab. Additionally, when a patient has comorbid atopic dermatitis or eosinophilic esophagitis, consider the use of dupilumab, whereas patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) may benefit from either dupilumab or mepolizumab.

Steroid dependency is 1 of the most pressing clinical problems in severe asthma, contributing significantly to morbidity over time. Both anti-IL5/5R α and dupilumab are effective in reducing the need for OCSs. The mean percentage reduction in OCSs with anti-IL5/5R α and dupilumab was 47% and 28%, respectively (e-Table S4). While there appears to be a difference between these classes of medications, the difference is likely explained by the variations in study populations and study design.¹⁵⁻¹⁷ In the dupilumab studies, patients were on 3 controller agents at the time of randomization suggesting more severe asthma compared to anti-IL5/5R α patients who were on 2 controller agents. In addition, patients in the placebo arm of the dupilumab study had a 42% reduction in steroid use compared to baseline, questioning the actual effectiveness of dupilumab in reducing OCS use.¹⁵

Both anti-IL5/5R α and dupilumab were equally effective in terms of exacerbation reduction (46% and 44%, respectively), FEV₁ improvement (approximately 140 mL each), asthma control as assessed by asthma control questionnaire (mean difference [MD], 0.28 vs 0.3 respectively) and QoL improvement as assessed by AQLQ (0.22 vs 0.28 respectively) (e-Table S4).

The risk of side effects was lower with anti-IL5/5R α compared to dupilumab (RR, 0.77 vs 1.05 respectively) (e-Table S4); however, given that differences could be explained by variations in baseline severity across studies, the panel suggests considering the patient's comorbidities and biomarker data to guide therapy as further detailed in the Discussion section.

PICO 3

Question 3: Should adult patients with steroid dependent asthma be treated with dupilumab or tezepelumab?

CHEST Recommendation: In adult patients with severe asthma who are steroid dependent, the panel suggests dupilumab over tezepelumab (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: This question could have also replaced dupilumab with anti-IL5/5R α noting the results from PICO 2. In summary, the clinician should consider either dupilumab or anti-IL5/5R α for OCS dependent asthma over tezepelumab. And the selection for either of these agents may be directed by pre-OCS AEC or other co-morbid conditions as noted above.

Both dupilumab and tezepelumab show improvement in key outcome measures; however, there are no direct comparisons of either agent to help guide clinicians. Tezepelumab provides greater reduction in asthma exacerbations compared to dupilumab (58% vs 44%) (e-Table S5). Dupilumab results in a greater reduction in OCS dosing (28% reduction when compared to the control group) as opposed to no effect in OCS dosing for tezepelumab (e-Table S5). Both dupilumab and tezepelumab result in an average FEV₁ improvement of 140 mL (e-Table S4). Neither agent showed a clinically meaningful improvement in asthma related QoL or asthma control scores (e-Table S5). There were slightly more observed side effects with dupilumab as compared to tezepelumab (RR, 1.05 vs 0.68) (e-Table S5). However, given the superior reduction in OCS reducing effects, dupilumab is conditionally recommended over tezepelumab.

PICO 4

Question 4: Should adult patients with moderate to severe asthma who have not demonstrated a clinical response to omalizumab after 4-6 months be treated with anti-IL5/5R α or dupilumab?

CHEST Recommendation: In adult patients with moderate to severe asthma who have not demonstrated a clinical response to omalizumab after

4-6 months, the panel suggests either anti-IL5/5R α therapy or dupilumab (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: Due to limitations in PICO formatting, it is worth mentioning that tezepelumab would also be a reasonable option to consider. Both anti-IL5/5R α and dupilumab perform similarly with regards to primary outcome measures, and thus selection is likely influenced by other factors as already mentioned in the PICO 2 remarks. In addition to considering pre-OCS AEC and co-morbidities, the clinician may consider the use of FENO. The rate of exacerbation reduction with dupilumab was proportional to FENO such that higher FENO values portended a large reduction in exacerbations. Anti-IL5/5R α agents have not been shown to affect FENO levels or predict outcomes in clinical trials.

A patient who achieves a good clinical response to a biologic is generally considered to have had at least a 50% reduction in exacerbations when compared to their baseline exacerbation rate, and at least a 50% reduction in the maintenance OCS dose. Individuals who achieve a 50% exacerbation reduction without a change in OCS requirements are also considered have a good clinical response.¹ In patients who do not demonstrate an appropriate clinical response by 4-6 months, a switch of biologic agents is usually recommended. Since the introduction of omalizumab for asthma, there are several newer agents that may be appropriate for patients who continue to experience ≥ 2 exacerbations annually.

There is no difference in exacerbation reduction between anti-IL5/5R α therapy and dupilumab (46% vs 44 % respectively) (e-Table S6). Similarly, there was no significant difference found in QoL metrics (MD, 0.22 vs 0.28), change in FEV₁ (approximately 140 mL each), or OCS reduction (47% vs 28%) (e-Table S6). The committee did not feel the steroid sparing effect was substantially different between the 2 agents. The lower OCS sparing effect noted in dupilumab was largely driven by the significant OCS sparing effect in the placebo group. To help the clinician select between these 2 agents, the panel suggests taking into consideration other co-morbid conditions as well as measuring FENO which is further elaborated on in the Discussion section.

PICO 5

Question 5: Should adult patients with severe asthma who have not demonstrated a clinical response to anti-

IL5/5R α after 4-6 months be treated with dupilumab or tezepelumab?

CHEST Recommendation: In adult patients with severe asthma who have not demonstrated a clinical response to anti-IL5/5R α therapy after 4-6 months, the panel suggests either dupilumab or tezepelumab (Conditional Recommendation, Very Low Certainty of Evidence).

A. For patients who are steroid dependent, the panel suggests dupilumab over tezepelumab (Conditional Recommendation, Very Low Certainty of Evidence).

Patients for whom 1 biologic in the anti IL5/5R α class fails could potentially be considered for another agent within the same class; however, considering the similar mechanisms of action, it is generally recommended to consider switching to an agent with a different mechanism of action.

Tezepelumab provides a greater reduction in asthma exacerbations compared to dupilumab (58% vs 42% reduction) (e-Table S7). However, this difference could be explained by differences in disease severity across study populations, given that at the time of randomization, patients enrolled in the dupilumab group were on 3 controller agents whereas the majority (90.6%) of patients in the tezepelumab group were on 2 controller agents.^{18,19} Asthma control, QoL, FEV₁, and adverse events were previously reported in PICO 3.

Dupilumab is conditionally recommended over tezepelumab in patients who are OCS dependent or have OCS related complications.¹⁵ Dupilumab is associated with a 28% reduction in OCS dose when compared to placebo with higher rates of OCS reduction observed in those with AEC ≥ 300 cells/ μ L. In contrast, no OCS reduction was noted with tezepelumab.²⁰

PICO 6

Question 6: Should adult patients with severe asthma who have not demonstrated a clinical response to dupilumab after 4-6 months be treated with anti-IL5/5R α or tezepelumab?

CHEST Recommendation: In adult patients with severe asthma who have not demonstrated a clinical response to dupilumab after 4-6 months, the panels suggests either anti-IL5/5R α or tezepelumab (Conditional Recommendation, Very Low Certainty of Evidence).

A. For patients who are steroid dependent, the panel suggests anti-IL5/5R α (Conditional Recommendation, Very Low Certainty of Evidence).

Remarks: For patients who are non-OCS dependent, the clinician may consider pre-biologic treatment AEC or FENO to help guide therapy. Dupilumab primarily targets T2 mediated inflammation whereas tezepelumab targets both T2 high and low inflammation. Thus, patients who exhibit primarily low AEC, low FENO, or both prior to initiation of biologic therapy may confer benefit with tezepelumab due to differences in mechanism of action.

Dupilumab is commonly used for patients who exhibit a T2 high endotype; however, it is worth mentioning that there was an improvement in exacerbations in individuals with a T2 low endotype (FENO < 25 ppb) although it did not reach statistical significance. Anti-IL5/5R α agents are only considered for patients with T2 high asthma. Tezepelumab, on the other hand, exhibits a significant reduction in exacerbations in both T2 high and T2 low individuals; however, the magnitude of response is still greater in those individuals exhibiting a T2 high endotype. For patients who have not demonstrated a clinical response to dupilumab, additional guidance is needed.

The reduction in asthma exacerbation was slightly better for tezepelumab as compared to anti-IL5/5R α (58% vs 46% respectively) (e-Table S8). There was no difference observed in asthma control (MD, 0.28 vs 0.33 respectively), QoL based on AQLQ score (MD, 0.22 vs 0.25 respectively), or FEV₁ (approximately 140 mL each) (e-Table S8). However, there was a greater steroid sparing effect with anti-IL5/5R α as compared to tezepelumab (47% reduction vs 0% respectively when compared to placebo) (e-Table S8).

Thus, for patients who are OCS dependent, anti-IL5/5Ra is suggested, largely owing to the superior OCS sparing ability. However, for patients who are not OCS-dependent, but continue to experience high rates of exacerbations, the selection may be further influenced by baseline biomarkers and co-morbid conditions. Further remarks regarding co-morbid conditions that may influence selection are in the Discussion section.

PICO 7

Question 7: Should FENO be used for guiding changes in therapy to dupilumab in adult patients with severe asthma on anti-IL5/5R α have not demonstrated a clinical response by 4-6 months?

CHEST Recommendation: In adult patients with severe asthma on anti-IL5/5R α who have not demonstrated a clinical response by 4-6 months, the panel suggests the use of posttreatment FENO $\geq$ 25 ppb for advising changes in therapy to dupilumab (Conditional Recommendation, Very Low Certainty of Evidence).

Elevated FENO levels primarily reflect the stimulation of inducible nitric oxide synthase by cytokines IL4 and IL13 in airway epithelial cells and inflammatory cells and thus reflects a useful biomarker to assess in patients with severe asthma.²¹ To date, there remains heterogeneity regarding the widespread clinical adoption of FENO in the routine management of asthma. In carefully selected patients with moderate to severe asthma, dupilumab has been shown to decrease asthma exacerbations, reduce baseline OCS, and improve QoL and pre-bronchodilator FEV₁.^{15,18,22,23} At present, there are no randomized controlled trials that have evaluated the role of FENO in guiding switching to dupilumab in patients with asthma for whom anti-IL5/5R α therapy fails. There are indirect data to support the role of FENO in patients receiving dupilumab. At present, there are no randomized controlled trials that have evaluated the role of FENO in guiding switching to dupilumab in patients with asthma for whom anti-IL5/5R α therapy fails.

The pooled analysis of asthma exacerbation rate with dupilumab vs placebo stratified by baseline FENO reveals a significant difference in asthma exacerbation rate reduction between the subgroups with FENO < 25 ppb (17%) vs FENO $\geq$ 25 ppb (74%), *P* value < .001 (e-Table S9). Additionally, the pooled analysis of the prebronchodilator FEV₁ change with dupilumab vs placebo stratified by baseline FENO reveals significant difference in prebronchodilator FEV₁ improvement between the subgroups with FENO < 25 ppb (20 mL) vs FENO $\geq$ 25 to 50 ppb (150 mL) and FENO > 50 ppb (350 mL), *P* value < .001. Similarly, the pooled analysis of the OCS reduction with dupilumab vs placebo stratified by baseline FENO reveals a greater OCS reduction in FENO $\geq$ 25 ppb as compared to FENO < 25 ppb. A FENO < 25 ppb resulted in a 17% reduction in OCS, a FENO $\geq$ 25 to 50 ppb (36% reduction), and FENO > 50 ppb (33% reduction), *P* value < .001.

The data support the cost-effectiveness of FENO monitoring in asthma management,²⁴⁻²⁸ but the panel did not formally review the cost-effectiveness of baseline FENO in assessing the selection of biological

therapy. FENO testing is noninvasive, portable, and provides point of care data helpful in the management of asthma. The ability to implement FENO in daily clinical practice relies on the availability of testing equipment, support staff, and insurance coverage. There are significant implications for equity, as those who are uninsured or insured by agencies not approving FENO may face out-of-pocket costs precluding implementation into clinical use. When using this biomarker, it is important to consider other factors such as obesity, pregnancy, and smoking that can affect FENO levels. An alternative to switching to dupilumab in non-responders to anti-IL5/5R α could be tezepelumab which has also shown improved outcomes in patients with elevated baseline FENO.¹⁹

Discussion

This guideline aims to give recommendations on the best way to choose biologics for treating severe asthma and also guide biologic switching, based on current evidence. Once clinicians accurately diagnose asthma, they should follow appropriate step-up guidance provided by currently available clinical practice guidelines.²⁹ Some patients, despite escalations in therapy, may continue to exacerbate necessitating biologics. While there are studies available to help guide the clinician for initial biologic selection,^{1,2,4-7,11,12} to date, there is no published guideline to assist in biologic selection when a patient has tried and failed 1 or more biologics. When a patient is not demonstrating a good clinical response to a prescribed biologic therapy, the clinician should pay careful attention to ensure the patient is also reassessed for adequate medication adherence and technique, modifiable risk factors, and co-morbid conditions, as well as appropriateness of the asthma diagnosis. According to panel consensus, patients who do not demonstrate a good clinical response after 4-6 months should be considered for a switch in biologics.

Selecting the most appropriate biologic agent can be challenging owing to the similarities among these agents as they target similar T2 mediated pathways and result in similar exacerbation reduction. However, up to 10% of patients do not demonstrate a good clinical response requiring a change in biologic therapy.³⁰ When selecting the most appropriate therapy, it is often helpful to first consider a patient's OCS dependency. For patients on maintenance OCSs, the panel suggests considering either anti-IL5/5R α or dupilumab due to OCS sparing capabilities. Further selection may be

refined to favor anti-IL5/5R α for patients who have intense peripheral eosinophilia (AEC > 1,500 cells/ μ L) to minimize the risk of hypereosinophilic-related complications seen with dupilumab.³¹ Indeed, patients who are OCS dependent will often not exhibit a significant elevation in the AEC due to OCS apoptotic effects of eosinophils, and thus it is important to assess pre-OCS AEC whenever possible to understand the intensity of this eosinophilia. For patients who have a pre-OCS AEC <1,500 cells/ μ L but currently require OCSs to maintain control, the panel recommends consideration of co-morbid conditions for agent selection. When selecting the most appropriate therapy, it is advisable to consider the other co-morbid approvals of several biologics, as shown in Table 3.

For non-OCS dependent patients, there is no clear or definitive difference in exacerbation reduction between the agents, although it is important to note that there were no head-to-head comparisons. Tezepelumab did exhibit the strongest exacerbation reduction when compared to placebo. In addition to considering co-morbid conditions, the panel also makes the recommendation to consider use of FENO. While the blood eosinophil count is a useful biomarker to diagnose eosinophilic asthma, it does not provide any discriminating data to help the clinician select the best agent. However, higher peripheral eosinophil counts are associated with a greater magnitude of exacerbation reduction for almost all of the agents. FENO may help differentiate between some of the available choices. A FENO $\geq$ 25 ppb is associated with a significant reduction in exacerbations with both dupilumab and tezepelumab. The magnitude of response is even greater when FENO is > 50 ppb for both agents. Anti-IL5/5R α therapy has not been shown to have an effect on FENO or predict outcomes in randomized controlled clinical trials.^{32,33} Limited data exist in the form of real-world studies on switching from a previous biologic to dupilumab. In a retrospective analysis of 38 patients with asthma who were switched from omalizumab or anti-IL5/5R α therapy to dupilumab, patients with FENO $\geq$ 25 ppb were more likely to respond compared to those with FENO < 25 ppb.³⁴ In other smaller studies, FENO levels reduced after dupilumab use but did not predict response.^{35,36} Tezepelumab is the only agent that has shown a significant reduction in exacerbations in patients with AEC <150 cells/ μ L and FENO < 25 ppb. An extension study examining patients from 2 studies affirmed asthma reduction at 104 weeks.³⁷

TABLE 3] Biologics for Use in Moderate to Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Mechanism of action	Anti-IgE	Anti-IL5	Anti-IL5	Anti-IL5R α	Anti-IL4R α /13	Anti-TSLP
Criteria for initiation ^a	Uncontrolled symptoms of allergic asthma with sensitization to perennial aeroallergen despite ICS use	Eosinophilic asthma (AEC $\geq$ 150 cells/ μ L) with exacerbation ($\geq$ 2 per year) despite use of ICS-LABA	Eosinophilic asthma (AEC $\geq$ 400) with exacerbation despite use of at least medium dose ICS	Eosinophilic asthma (AEC $\geq$ 300) with exacerbation ($\geq$ 2 per year) despite use of medium to high dose ICS-LABA	Eosinophilic asthma (AEC $\geq$ 150) with steroid dependency or with exacerbation despite use of medium to high dose ICS-LABA	Uncontrolled asthma with exacerbation despite use of medium to high dose ICS-LABA, T2 high or low asthma
Mode of administration	Subcutaneous	Subcutaneous	IV	Subcutaneous	Subcutaneous	Subcutaneous
Dosing and dosing interval	Every 2 or 4 wks, based upon pre-dosing IgE level and body weight	100 mg every 4 wks	Weight based every 4 wks	30 mg every 4 wks $\times$ 3, then every 8 wks thereafter	200 mg or 300 mg every 2 wks (consider loading dose)	210 mg every 4 wks
Co-morbid conditions with FDA approval	CRSwNP; chronic spontaneous urticaria; IgE mediated food allergies	CRSwNP; EGPA/HES (300 mg monthly dosing regimen)	N/A	EGPA (monthly dosing regimen)	Atopic dermatitis; CRSwNP; eosinophilic esophagitis (300 mg weekly dosing for > 40 kg), COPD (AEC $\geq$ 300 cells/ μ L)	CRSwNP (FDA approval pending)

AEC = absolute eosinophil count; CRSwNP = chronic rhinosinusitis with nasal polyposis; EGPA = eosinophilic granulomatosis with polyangiitis; FDA = US Food and Drug Administration; HES = hyper-eosinophilic syndrome; ICS = inhaled corticosteroid; IL-4R α = IL-4 receptor alpha subunit; LABA = long-acting beta-agonist; N/A = not applicable; TSLP = thymic stromal lymphopoietin.

^aBased upon US FDA criteria.

TABLE 4] Biologic Adverse Events and Monitoring Recommendations

Biologic	Unique or Serious Adverse Events	Serious Adverse Events (Relative Risk)	Monitoring Recommendations
Omalizumab	Anaphylaxis	0.81 (0.64-1.03)	Epinephrine auto-injector, consider first 3 doses observed in health care setting before transitioning to at-home administration
Mepolizumab	Herpes zoster	0.77 (0.65-0.91) pooled	No specific recommendation
Reslizumab	Anaphylaxis	0.77 (0.65-0.91) pooled	Epinephrine auto-injector
Benralizumab	None	0.77 (0.65-0.91) pooled	No specific recommendation
Dupilumab	Conjunctivitis keratitis hypereosinophilic complications; EGPA – rare case reports	1.05 (0.80-1.38)	Absolute eosinophil count (consider withdrawal of treatment or co-administration with anti IL5/5R α , consider short-term OCSs for asymptomatic eosinophilia > 3,000 cells/ μ L and frequent monitoring), recommend frequent OCS monitoring during OCS withdrawal
Tezepelumab	None	0.68 (0.54-0.85)	No specific recommendation

EGPA = eosinophilic granulomatosis with polyangiitis; OCS = oral corticosteroid.

And finally, it may be important to consider the injection frequency when selecting the agent if there is otherwise no clear choice. For patients who are particularly averse to injections, benralizumab offers the least frequent maintenance dosing regimen at once every 8 weeks. This is compared to the other biologics listed in [Table 3](#).

Each of the biologic agents used for treatment of moderate to severe asthma have overlapping and distinct adverse events, which are detailed in [Table 4](#). Common and overlapping adverse reactions for all the biologics include local injection site reactions, upper respiratory tract infections (nasopharyngitis), and hypersensitivity reactions. Hypersensitivity reactions can vary from mild to severe and include urticaria and angioedema. Local injection site reactions are the most common with pain, redness, swelling, and itching at the injection site, higher when administered subcutaneously than intravenously. These are generally mild and self-limiting.

All biologics have demonstrated a good safety profile, and the risk of serious adverse events is small. However, there is a need for regular monitoring of patients. For omalizumab, where anaphylaxis has been reported, the committee recommends considering observed monitoring in a health care setting for the first 3 doses while always having immediate access to an epinephrine auto-injector before transition to at-home administration. Reslizumab is limited to an infusion center due to requirement for IV infusion. Frequent monitoring for helminthic infestation is necessary, especially in population residing in endemic areas for all biologics except omalizumab.³⁸ Dupilumab does require

monitoring of blood eosinophils, particularly within the first few months of therapy as there is a risk of hypereosinophilia. This risk is usually more pronounced in patients with higher baseline AEC levels. Eosinophil levels are expected to peak at about 3-6 months' post initiation for biologic naive patients and often trend down subsequently.³⁵ In the vast majority of cases, the eosinophilia is asymptomatic and does not warrant discontinuation of the drug. Patients who are OCS dependent may need closer monitoring of their eosinophil count as the OCS dose is reduced. An extension study on tezepelumab confirmed low risk of severe adverse events at 104 weeks consistent with earlier studies.³⁷

One important limitation of this guideline is the decision to combine all anti-IL5/5R α into a single biologic class rather than treating them as individual agents. There are significant differences in the mode of action and pharmacology of the 3 biologics targeting the IL-5 pathway, with benralizumab achieving a depletion of eosinophils that is much greater than other monoclonal antibodies targeting the IL-5R α pathway, while reslizumab has greater potency in vitro for IL-5 binding as compared to mepolizumab.^{17,39-41} However, data from clinical trials coupled with real world evidence show that these biologic agents have similar clinical efficacy. For all 3 anti-IL5/5R α biologics, the higher the blood eosinophils, the higher the expected impact on asthma-related outcomes. Consequently, the guideline panel decided to evaluate them as a single class of drugs. Furthermore, this guideline does not exhaust all potential biologic failures and switches. The

decision to group all anti-IL5/5R α agents into 1 class limits the ability to consider switching within the same class. Patients who have not demonstrated clinical improvement with mepolizumab have shown significant improvements in exacerbation reduction and OCS reduction when switched to benralizumab.³⁰

All the recommendations formulated in this guideline are conditional, and their implementation by health care professionals and systems depends on several factors which can be found in the supplementary appendix (e-Table S10). Furthermore, implementation may be limited as a result of variable access to medications or diagnostic testing (FENO).

Interpretation

Several biologics are effective and approved for clinical use for patients with poorly controlled severe asthma despite adhering to standard of care inhaled and oral therapies. Given that there are currently no comparative effectiveness studies, nor is there a validated, commonly agreed definition of clinical response, biological therapies can only be individualized in daily practice using indirect comparisons of data (delineated into conditional recommendations). Decisions as to how individualize biological therapy should occur under a shared decision-making process that carefully considers underlying asthma co-morbidities, T2 biomarkers, injection frequency, mode of administration, and access to resources.

Financial/Nonfinancial Disclosures

The conflict of interest statements are available online under “Supplementary Data.”

Acknowledgments

Author contributions: M. M. had full access to all the data in the study of the data and the accuracy of the data analysis. A. J. O. served as the principal author and gave final approval of the version to be published. F. H. served as the senior author. A. J. O., M. M., and F. H. take accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. All authors contributed to drafting the work or reviewing it critically for important intellectual content.

Other contributions: The authors appreciate medical librarian Lorraine Porcello for assistance in the literature search strategy.

Additional information: The e-Appendix, e-Figure, and e-Tables are available online under “Supplementary Data.”

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