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Biologic Therapy in Severe Asthma: A Practical Framework for Initial Selection and Switching

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ABSTRACT

Severe asthma is a heterogeneous clinical syndrome in which poor symptom control, recurrent exacerbations, and substantial corticosteroid exposure persist despite optimized inhaled therapy and appropriate correction of modifiable factors. Biologic therapy has transformed outcomes for many patients with type 2 inflammation; however, real-world selection remains challenging because allergic and eosinophilic traits frequently overlap, biomarkers fluctuate over time, and definitive head-to-head comparative trials are limited. This practical narrative review addresses two core clinical questions: how to phenotype severe asthma in routine care, and how to choose the most appropriate biologic according to biomarker pattern, exacerbation burden, oral corticosteroid dependence, and major comorbidities. We outline a clinic-ready framework that begins with confirmation of true severe asthma and exclusion of pseudo-severe disease caused by poor adherence, incorrect inhaler technique, persistent exposures, or untreated comorbidity. Readily available biomarkers, including blood eosinophils, fractional exhaled nitric oxide (FeNO), total serum IgE, and allergen sensitization, are reviewed with emphasis on both their usefulness and their limitations. We then summarize the evidence for anti-IgE, anti-IL-5, anti-IL-5Rα, anti-IL-4Rα, anti-TSLP, and ultra-long-acting anti-IL-5 therapy, highlighting practical cues from pivotal trials and contemporary guideline frameworks. A phenotype-guided, treat-to-target strategy can improve biologic matching, reduce severe exacerbations, support safer corticosteroid tapering, and justify timely switching when the initial response is inadequate.

Keywords: severe asthma; difficult-to-treat asthma; biologic therapy; phenotype; endotype; treatable traits; eosinophils; FeNO; IgE; type 2 inflammation.

Abbreviations:

ACT, Asthma Control Test
CRSwNP, chronic rhinosinusitis with nasal polyps
FeNO, fractional exhaled nitric oxide
ICS, inhaled corticosteroid
ILC2, type 2 innate lymphoid cell
ILD, interstitial lung disease
LABA, long-acting beta 2-agonist
OCS, oral corticosteroid
RCT, randomized controlled trial
TSLP, thymic stromal lymphopoietin.

Introduction

Severe asthma represents the most burdensome end of the asthma spectrum. Although it affects only a minority of patients, it accounts for a disproportionate share of exacerbations, emergency visits, hospitalizations, impaired quality of life, work loss, and cumulative systemic corticosteroid exposure.[1-4] Current guidance distinguishes severe asthma from merely difficult-to-treat asthma: the diagnosis should be reserved for patients who remain uncontrolled despite high-dose ICS/LABA-based therapy after adherence, inhaler technique, environmental exposures, and major comorbidities have been systematically addressed.[1-3]

The clinical question has therefore shifted from asking whether biologics work to deciding which biologic best matches a given patient. Anti-IgE, anti-IL-5, anti-IL-5Rα, anti-IL-4Rα, and anti-TSLP therapies each occupy a biologically plausible niche, but real-world patients rarely present with a single isolated endotype. A patient with recurrent exacerbations may simultaneously have allergic sensitization, fluctuating eosinophilia, elevated FeNO, obesity, chronic rhinosinusitis, and intermittent oral corticosteroid exposure. In this setting, precision medicine must be practical, reproducible, and anchored to everyday clinic decisions rather than to theory alone.[4-12]

Accordingly, this article is designed as a practical narrative review for clinicians. Its purpose is not to catalogue every speculative biomarker or every early-phase molecule in equal detail, but to provide a usable framework for initial biologic selection and reassessment that is grounded in pivotal trials, contemporary guidelines, and routine severe-asthma practice.[1-4,9,12]

Confirming true severe asthma before biologic selection

Before any biologic is prescribed, the clinician must confirm that the patient truly has severe asthma rather than uncontrolled disease driven by remediable factors. GINA and ERS/ATS guidance consistently emphasize this step because biologics deliver their greatest value only when they are added to a correct diagnosis and an optimized treatment background.1-3

At minimum, the evaluation should document objective evidence of variable airflow limitation; verify that high-dose ICS/LABA therapy is appropriate for the individual patient; and directly review device selection, inhaler technique, and adherence, which remain among the commonest causes of pseudo-severe asthma.[1, 2] Pharmacy refill history, dose counters, and structured inhaler observation are often more informative than patient recall alone.

The clinician should also define the domains of poor control: symptom burden, reliever use, exacerbation frequency, lung function impairment, and oral corticosteroid requirement. Biologic eligibility should be documented only after high-dose controller therapy has been optimized and modifiable drivers of poor control have been actively identified and treated.[1-3]

Treatable traits framework: the practical gateway to precision medicine

The treatable-traits model provides a pragmatic bridge between pathobiology and bedside decision-making. Rather than viewing asthma as a single disease label, this framework identifies measurable and modifiable traits that materially influence outcomes.[5,10,11] In severe asthma, these include confirmation of the diagnosis itself, poor adherence or incorrect inhaler technique, smoking or occupational exposure, eosinophilic inflammation, allergic sensitization, upper-airway disease, obesity-related asthma, sleep-disordered breathing, recurrent infection, and steroid toxicity (Table 1).

The strength of this approach is that it integrates inflammatory and non-inflammatory burdens. A patient with eosinophilic asthma and chronic rhinosinusitis with nasal polyps may justifiably receive a different biologic from a patient with a similar eosinophil count but no upper-airway disease and substantial corticosteroid toxicity. Likewise, the presence of bronchiectasis or recurrent lower-airway infection should recalibrate expectations because not every exacerbation in such patients is biologically driven or highly responsive to anti-type 2 therapies.[4,5,10]

Table 1. Treatable traits and practical identification points to avoid pseudo-severe asthma.

Domain	Treatable trait	How to identify (clinic-ready)	Why it matters for biologics/outcomes
Diagnosis	Not asthma/alternative diagnosis	Objective testing; consider ILO/VCD, COPD, HF, bronchiectasis, ILD	Avoid ineffective escalation; directs the correct pathway [1, 2].
Treatment factors	Poor adherence/wrong technique	Direct observation; refill history; device mismatch	Common cause of pseudo-severe asthma; optimize before biologic selection.[1,2]

Domain	Treatable trait	How to identify (clinic-ready)	Why it matters for biologics/outcomes
Exposure	Smoking/vaping; occupational irritants	History; cotinine if needed; workplace review	Lowers ICS response, increases exacerbations, and may blunt biologic benefit.[1,2]
Type 2 inflammation	Eosinophilia	Blood eosinophils (repeat if steroid-exposed)	Predicts response to IL-5/IL-5Rα and often IL-4Rα blockade.[9,15]
Type 2 inflammation	IL-4/IL-13 signal	FeNO (interpret confounders; repeat)	Predicts response to IL-4Rα blockade and supports a type 2 endotype.[1,2,15]
Allergy	Clinically relevant sensitization	Total/specific IgE, skin testing; exposure linkage	Supports anti-IgE selection when the allergic phenotype is dominant [9, 15].
Upper airway	CRSwNP/chronic rhinosinusitis	ENT assessment; symptom scores; nasal endoscopy if available	Often influences biologic choice (dual benefit for asthma and upper-airway disease).[2,9,15]
Sleep/metabolic	OSA/obesity-related asthma	STOP-BANG; sleep study; BMI/waist	Treating reduces symptom burden and improves response assessment [1, 2].
GI	GERD	Typical symptoms; selective testing	May reduce cough and wheeze burden and prevent overtreatment.[1,2]
Airway infection	Bronchiectasis/recurrent infection	CT when indicated; sputum culture history	Affects exacerbation phenotype and impacts expectations and adjunctive strategies [1, 2].
Steroid toxicity	OCS-related harm	Weight, BP, glucose, bone risk, cataracts	Drives an urgent steroid-sparing strategy and biologic prioritization [1, 2, 15].

Biomarkers and endotype definition in routine care

In everyday practice, the most useful biomarkers remain blood eosinophils, FeNO, total serum IgE, and clinically relevant allergen sensitization (Table 2). None is sufficient in isolation, but taken together they help define whether Type 2 inflammation is present and which pathway appears most dominant.[4,5,9] Blood eosinophils remain the most practical surrogate for eosinophilic inflammation and are particularly relevant when considering IL-5 or IL-5 receptor blockade. Recurrent eosinophilia, especially in exacerbation-prone disease, strongly supports an eosinophilic phenotype.[1,2,7,9]

FeNO reflects IL-4/IL-13-driven airway inflammation and is especially informative when blood eosinophils are suppressed by recent systemic corticosteroid exposure. Persistently elevated FeNO strengthens the case for ongoing type 2 activity and often points toward **IL-4Rα** blockade, particularly when upper-airway or atopic comorbidity is present.[4, 12] Serum total IgE should not be misinterpreted as a stand-alone predictor of response; its primary value is confirming eligibility for anti-IgE therapy when combined with clear sensitization and a clinically relevant allergic phenotype.[1, 2, 4, 7, 9, 11, 13]

All biomarkers must be interpreted in context. Systemic corticosteroids can suppress eosinophils and FeNO; smoking can blunt FeNO interpretation; and parasitic infection, vasculitis, or hematologic disease can cause eosinophilia that is not asthma-related. Repeated measurements obtained during clinical stability are often more informative than a single result captured during infection, an exacerbation, or immediately after a steroid burst.[1, 2]

An apparently biomarker-low profile should therefore be interpreted cautiously. In severe asthma, persistently low eosinophils and FeNO may reflect suppression by high-dose ICS or OCS rather than truly absent type 2 biology. When a patient remains symptomatic or exacerbation-prone despite serially low biomarkers, the clinician should re-examine corticosteroid exposure and alternative drivers such as smoking, obesity, dysfunctional breathing, inducible laryngeal obstruction, infection, or mucus-predominant disease before labeling the case as genuinely T2-low.[9,36]

Table 2. Biomarkers and practical phenotype-defining signals in severe asthma.

Signal	How to assess	What it suggests	Important caveat
Total IgE + sensitization	Total IgE with specific IgE/skin testing and exposure history	Allergic phenotype; supports anti-IgE when clinically relevant	IgE alone does not predict response; relevance of sensitization matters
Blood eosinophils	Repeat CBC during clinical stability	**Eosinophilic endotype; supports anti-IL-5/IL-5R and often anti-IL-4Rα**	Suppressed by recent systemic steroids; a low single value may misclassify
FeNO	Point-of-care exhaled nitric oxide	IL-4/IL-13 signal; supports type 2 inflammation and dupilumab selection	Affected by ICS use, smoking, infection, and timing

Signal	How to assess	What it suggests	Important caveat
Comorbid CRSwNP/atopy	History, ENT evaluation, dermatologic review	May shift selection toward dupilumab or strengthen type 2 phenotype	Comorbidity benefit should complement, not replace, asthma goals

To bridge biomarker-defined endotypes with the subsequent mechanism-based treatment discussion, Figure 1 provides a conceptual roadmap linking airway epithelial injury and type 2 inflammation to the principal biologic targets used in severe asthma[1,2,4,9,12,32].

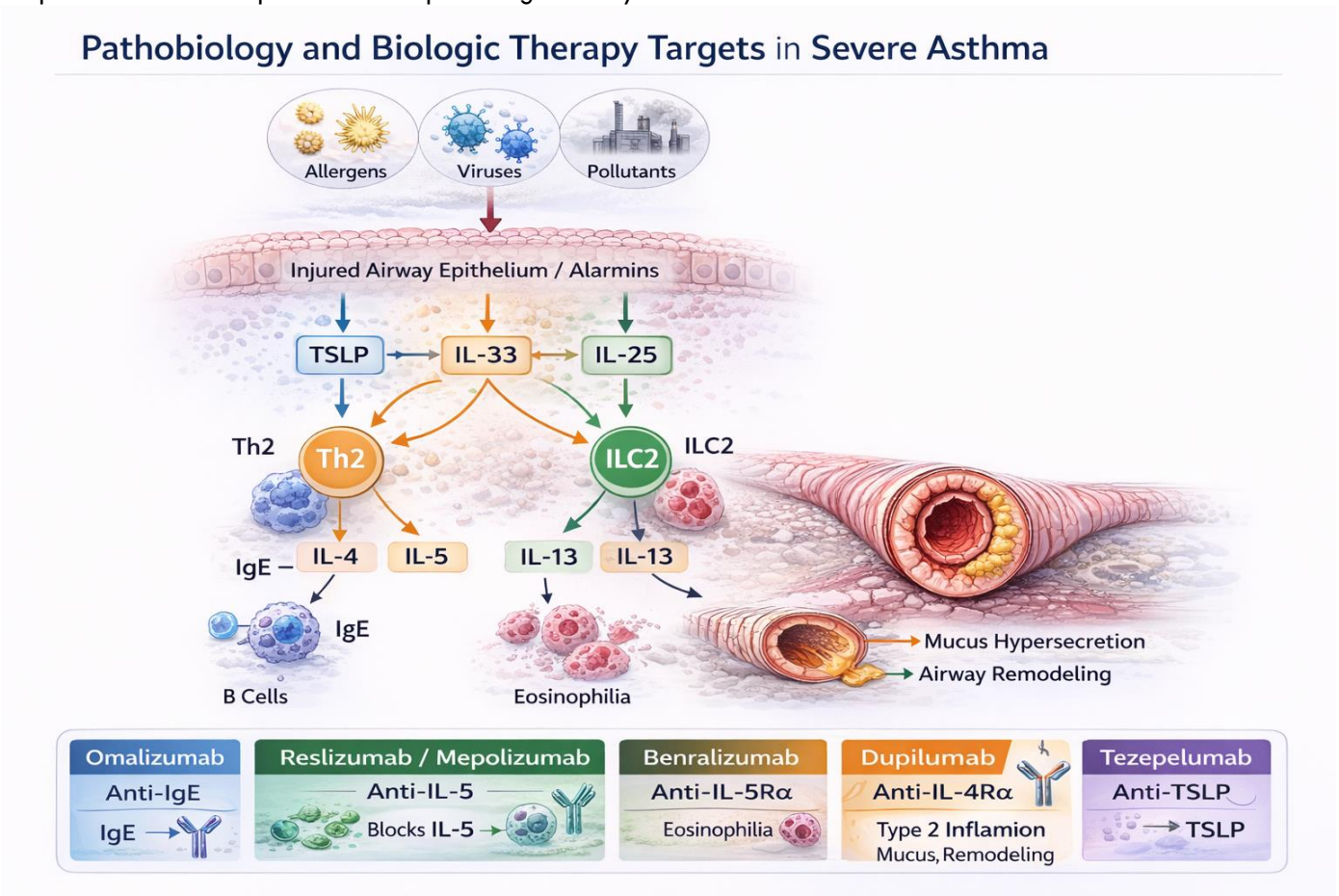

Figure 1. Simplified pathobiology of severe asthma and major biologic targets. Airway epithelial injury triggers release of alarmins that activate Th2 and ILC2 pathways, leading to IL-4, IL-5, and IL-13 signaling, IgE production, eosinophilic inflammation, mucus hypersecretion, and airway remodeling. The figure also summarizes the principal biologic targets: **IgE, IL-5, IL-5Rα, IL-4Rα, and TSLP.**[1,2,4,9,12,32]

Evidence-Based Biologic Classes

Biologic selection should reflect dominant biology, exacerbation burden, oral corticosteroid exposure, and key comorbidities rather than any single biomarker viewed in isolation. Each established biologic class has a recognizable clinical niche that is supported by randomized trials and reinforced by real-world experience. Figure 1 and Table 3 are intended to simplify this logic by linking mechanism to the most relevant bedside selection cues.[4,9,11,12]

Anti-IgE therapy: omalizumab

Omalizumab remains the prototype biologic for severe allergic asthma. Its clearest rationale is in patients with clinically meaningful perennial sensitization, IgE values within the approved dosing range, and persistent exacerbations despite optimized inhaled therapy.[4, 13, 14] Omalizumab consistently reduces exacerbations and improves asthma control, whereas improvements in lung function are usually more modest. The best responses are seen when allergy is a true driver of disease rather than an incidental laboratory finding.[13, 14]

Anti-IL-5 and anti-IL-5Rα therapy: mepolizumab, reslizumab, benralizumab, and depemokimab

Mepolizumab, reslizumab, and benralizumab are the principal biologics targeting the eosinophilic axis in severe asthma. Mepolizumab reduced exacerbations in DREAM and MENSA and demonstrated clinically important oral corticosteroid-sparing efficacy in SIRIUS. Benralizumab significantly reduced exacerbations in SIROCCO and CALIMA and showed robust steroid-sparing benefit in ZONDA. Reslizumab also reduced exacerbations in eosinophilic disease, although its role is more limited in many settings because it is administered intravenously and requires attention to infusion-related hypersensitivity and anaphylaxis precautions.[15-22]

In routine practice, IL-5 pathway therapy is often the most straightforward option when recurrent exacerbations and blood eosinophilia dominate the clinical picture. These agents are particularly attractive in adult-onset eosinophilic asthma and in patients with a substantial oral corticosteroid burden. Benralizumab offers the additional mechanistic advantage of rapid and near-complete

blood eosinophil depletion through antibody-dependent cell-mediated cytotoxicity, which may be useful when brisk eosinophil suppression is desired.[4,9,12,18-20,30]

Depemokimab extends the same biologic logic through ultra-long-acting IL-5 neutralization. The phase 3 SWIFT-1 and SWIFT-2 trials demonstrated significant exacerbation reduction with twice-yearly dosing in severe eosinophilic asthma, making depemokimab a potentially valuable option when adherence, injection burden, or visit frequency materially affect real-world treatment persistence. Where approved and available, it should be regarded as an additional IL-5-directed option rather than as a separate mechanistic class.[31]

Anti-IL-4Rα therapy: dupilumab

Dupilumab blocks signaling through the IL-4 receptor alpha subunit and thereby inhibits both IL-4 and IL-13 pathways. In the LIBERTY ASTHMA QUEST trial, dupilumab reduced severe exacerbations and improved lung function, with the greatest benefit observed in patients with heightened type 2 inflammation.[23,24] In the LIBERTY ASTHMA VENTURE trial, dupilumab also reduced maintenance oral corticosteroid use in glucocorticoid-dependent severe asthma.[25] Similar signals were reported in the earlier phase 2b study.[34]

Clinically, dupilumab is especially attractive when asthma coexists with chronic rhinosinusitis with nasal polyps or atopic dermatitis, because one therapy may simultaneously improve multiple type 2-driven manifestations.[4,12] It is also a strong option when FeNO remains elevated despite corticosteroid therapy. The principal caution is treatment-emergent eosinophilia, which is usually transient and asymptomatic but can occasionally be clinically relevant.[23-25]

Table 3: Biologic classes in severe asthma: targets, best-fit signals, and practical selection cues.

Class/agent	Target	Best-fit phenotype/signal	Practical selection cues	Evidence highlights (high level)
Anti-IgE (omalizumab)	IgE	Allergic severe asthma	Clinically relevant sensitization + dosing eligibility; link exposure to symptoms	Reduces exacerbations in severe allergic asthma; greatest benefit when allergic drivers are clear.[13,14]
Anti-IL-5 (mepolizumab; reslizumab)	IL-5	Eosinophilic asthma	Elevated/recurrent eosinophilia; exacerbation-prone; OCS-sparing need	Robust exacerbation reduction; OCS-sparing shown for mepolizumab in steroid-dependent eosinophilic asthma.[15-17,21,22]
Anti-IL-5Rα (benralizumab)	IL-5Rα	Eosinophilic asthma	Higher eosinophils and exacerbations; steroid-dependent patients	Exacerbation reduction and strong OCS-sparing evidence.[18-20]
Anti-IL-4Rα (dupilumab)	IL-4/IL-13 pathway	Type 2 asthma; OCS-dependent; ± CRSwNP/AD	Prioritize if OCS-dependent and/or CRSwNP/AD are major co-targets	Demonstrated OCS-sparing and improved outcomes in Type 2 asthma.[23-25,34]
Anti-TSLP (tezepelumab)	TSLP (alarmin)	Broad severe uncontrolled asthma	Useful when biomarkers are low/variable or phenotype is mixed	Reduced exacerbations across biomarker strata; SOURCE did not meet its primary OCS-sparing end point.[26-28]
Ultra-long-acting anti-IL-5 (depemokimab)	IL-5	Eosinophilic phenotype	Twice-yearly dosing may improve adherence and reduce treatment burden, where approved/available.	SWIFT trials showed exacerbation reduction with twice-yearly dosing; availability depends on regional regulatory approval.[31]

Upstream epithelial cytokine blockade: tezepelumab

Tezepelumab targets TSLP, an epithelial alarmin positioned upstream of several inflammatory cascades. This upstream location explains why it can retain efficacy even when the inflammatory picture is mixed or when eosinophil counts are not markedly elevated. In PATHWAY and NAVIGATOR, tezepelumab significantly reduced exacerbations and improved lung function across a broad severe-asthma population.[26,27]

Its broad efficacy makes tezepelumab particularly relevant when biomarkers are low, variable, or conflicting, and when a previous biologic has failed despite ongoing exacerbations. However, SOURCE did not demonstrate the same degree of oral corticosteroid-sparing efficacy seen with some other classes. Therefore, when chronic oral corticosteroid dependence is the dominant problem and eosinophilic signals are strong, many clinicians still prioritize IL-5 pathway therapy or dupilumab before tezepelumab.[28]

Choosing the Initial Biologic: A Practical Framework

The initial biologic should be selected only after a structured review of five domains:

1. Phenotype
2. Biomarker pattern
3. Exacerbation burden
4. Oral corticosteroid dependence
5. Major comorbidities.[1,2,4,9,12,32]

- Severe allergic asthma with clear perennial sensitization favors omalizumab.[1,2,12-14,32]
- Exacerbation-prone eosinophilic asthma, especially when adult-onset or steroid-dependent, favors anti-IL-5 or anti-IL-5Rα therapy—mepolizumab, reslizumab, benralizumab, or depemokimab.[4,9,12,15-22,31,32]
- High FeNO, chronic rhinosinusitis with nasal polyps, and atopic dermatitis increase the appeal of dupilumab. Mixed phenotypes, or biomarker-low but exacerbation-prone disease, support tezepelumab.[23-28,32]
- No currently available trial provides definitive head-to-head superiority across the large group of patients with overlapping traits. Selection therefore remains a reasoned clinical match rather than a rigid algorithm. This is not a weakness of phenotype-guided medicine; it is a reminder that biology, comorbidity profile, and the patient's most urgent unmet need must remain central to decision-making.[4,9,12,32]

Reassessment, Non-response, and Switching Strategy

Biologic success or failure should not be judged too early. Most guidelines and pivotal trials support formal reassessment after approximately 4 to 6 months, using a multidimensional definition of response that includes exacerbation frequency, symptom control, reliever use, lung function, oral corticosteroid reduction, and comorbidity outcomes. These goals should be defined before treatment begins. A biologic may still be considered successful even if FEV1 improves only modestly, provided that exacerbations and corticosteroid exposure fall meaningfully.[1,2,12]

Before labeling a patient a non-responder, the clinician should re-check adherence to inhaled and biologic therapy, inhaler technique, smoking or occupational exposure, obesity-related breathlessness, infection, and upper-airway disease control. Only after these issues have been revisited should switching be pursued, ideally toward a different mechanism that better matches the residual biomarker pattern and comorbidity profile.[1,2,9,10]

Switching should also be pattern-based rather than automatic. Breakthrough exacerbations on anti-IL-5 therapy are heterogeneous; persistent FeNO elevation or residual eosinophilic airway inflammation suggests ongoing type 2 activity and may support a switch toward an IL-4Rα- or upstream alarmin-directed strategy, whereas biomarker-low attacks should prompt reassessment for infection, poor inhaled adherence, or non-type 2 mechanisms.[9,38]

Guideline-informed comparative practice points

Recent CHEST clinical practice guidance provides a useful pragmatic overlay for biologic choice in adults with severe asthma. Comparative selection still rests largely on indirect evidence because head-to-head trials are lacking; accordingly, all seven recommendations were conditional and based on very low-certainty evidence. Even so, the guideline highlights clinically actionable domains beyond biomarker pattern alone, especially oral corticosteroid dependence, baseline lung function, exacerbation burden, quality-of-life impairment, and major comorbid type 2 conditions.[32]

In allergic severe asthma (Table 4), with at least one corticosteroid-treated exacerbation per year, either omalizumab or dupilumab is reasonable, but dupilumab becomes more attractive when exacerbations are more frequent or severe or when FEV1 is below 70% predicted. By contrast, omalizumab may remain a sound first choice when the dominant unmet need is allergic disease with disproportionate quality-of-life impairment rather than repeated severe exacerbations. In steroid-dependent disease (Table 4), recent guidance favors anti-IL-5/IL-5Rα therapy or dupilumab and generally places dupilumab ahead of tezepelumab when oral corticosteroid sparing is a primary goal.[32]

Table 4: Guideline-informed practical choice and switching cues from the CHEST 2026 clinical practice guideline.

Clinical situation	Preferred option(s)	Practical cue
Allergic severe asthma with ≥1 steroid-treated exacerbation/year	Omalizumab or dupilumab	Favor dupilumab if exacerbations are frequent/severe or if FEV1 < 70%; favor omalizumab when allergic disease with quality-of-life impairment predominates.
OCS-dependent severe asthma	Anti-IL-5/IL-5Rα or dupilumab	Dupilumab is generally preferred over tezepelumab when steroid-sparing is a major goal.
Inadequate response to omalizumab after 4-6 months	Anti-IL-5/IL-5Rα or dupilumab	Switch mechanism only after rechecking adherence, inhaler technique, and comorbidity control.
Inadequate response to anti-IL-5/IL-5Rα	Dupilumab or tezepelumab	In steroid-dependent disease favor dupilumab; post-treatment FeNO ≥25 ppb supports switching toward dupilumab.
Inadequate response to dupilumab	Anti-IL-5/IL-5Rα or tezepelumab	In steroid-dependent disease favor anti-IL-5/IL-5Rα.
T2-low or biomarker-low uncontrolled asthma	Tezepelumab	Particularly useful when eosinophils and FeNO are low, mixed, or conflicting.

Additional comparative clues may refine selection. Tezepelumab is particularly attractive in T2-low or biomarker-low severe asthma, whereas dupilumab may offer extra value when asthma coexists with chronic rhinosinusitis with nasal polyps, atopic dermatitis, or eosinophilic esophagitis. Conversely, very high pre-oral corticosteroid eosinophil counts (for example, >1,500/μL) may favor anti-IL-5/IL-5Rα therapy over

dupilumab because of the possibility of treatment-emergent hypereosinophilia. Among practical considerations, benralizumab offers the least frequent maintenance dosing, whereas omalizumab and reslizumab require greater attention to hypersensitivity and anaphylaxis monitoring.[32]

Special Clinical Scenarios

- Several clinical scenarios deserve explicit mention because they strongly influence biologic choice. First, oral corticosteroid-dependent asthma immediately elevates the importance of steroid-sparing evidence. SIRIUS, ZONDA, and VENTURE are particularly informative because they address the exact clinical question of whether maintenance steroid exposure can be reduced without destabilizing asthma control.[17,20,25]
- Second, chronic rhinosinusitis with nasal polyps is a major decision-shaping comorbidity. Both IL-5 pathway therapy and dupilumab may improve upper-airway disease, but dupilumab is often favored when FeNO is high or when nasal-polyp burden is clinically dominant.[4,12]
- Third, bronchiectasis overlap or recurrent infection should trigger caution before repeated escalation of anti-type 2 therapy, because not every flare in such patients is biologically driven.
- Fourth, pregnancy planning deserves explicit consideration. When more than one biologic is otherwise reasonable, omalizumab has the most reassuring human pregnancy safety experience, including registry data without an observed increase in major congenital abnormalities; the other biologics have less mature human pregnancy evidence, so initiation in women planning pregnancy is usually better anchored to the most established safety profile.[9,38]

When more than one biologic is reasonable, selection should be guided by the highest-value target and the most urgent unmet need. The patient's lived context also matters: dosing frequency, route of administration, home-injection confidence, access, reimbursement, and likelihood of persistence all influence the real success of precision medicine.[9,12]

Implementation in the Severe Asthma Clinic

A standardized severe-asthma pathway improves both clinical care and manuscript coherence. A practical workflow includes structured baseline intake; confirmation of exacerbation and oral corticosteroid history; direct observation of inhaler technique; biomarker testing timed in relation to steroid exposure; careful comorbidity review; shared decision-making; and formal reassessment after 4 to 6 months. These steps reduce pseudo-severe labeling and make biologic decisions more reproducible across clinicians.[1,2,5,9,10]

Regional epidemiology can also sharpen selection logic. In the Lebanese PREPARE study, eosinophilic severe asthma represented an important phenotype, reinforcing the clinical relevance of eosinophil-guided decision-making in local practice.[29]

Limitations and Evidence Gaps

Any phenotype-guided review of biologic therapy must acknowledge several limitations. Trial populations differ in baseline eosinophil thresholds, FeNO distributions, exacerbation definitions, background therapy, and inclusion criteria, making cross-trial comparisons imperfect. There are still no definitive head-to-head randomized trials that determine which biologic is best for a patient with overlapping allergic and eosinophilic traits.[4,12]

Biomarkers are dynamic rather than static and may be altered by corticosteroids, infection, or smoking. In addition, payer rules, availability, and local approval status often shape biologic choice almost as strongly as biology itself. These realities do not invalidate precision medicine; instead, they underscore the need for pragmatic frameworks that are both mechanism-based and implementable.

Looking ahead, biologic strategy may move beyond conventional control toward on-treatment clinical remission. Recent reviews suggest that approximately 20% to 40% of biologic-treated patients may achieve remission, and real-world cohorts have identified super-responder subgroups. Mucus plugging has also emerged as a clinically relevant phenotype associated with severity and impaired lung function, with early signals that dupilumab and tezepelumab may reduce mucus plugging in selected patients.[9]

Conclusion

Biologic therapy in severe asthma is most effective when applied through a practical, auditable framework for initial selection and reassessment. The clinician should first confirm true severe asthma, then identify treatable traits and interpret accessible biomarkers within the appropriate clinical context. Initial biologic choice should be guided by the dominant biology and clinical burden: anti-IgE therapy for clearly allergic disease; anti-IL-5 or anti-IL-5Rα therapy for eosinophilic, exacerbation-prone, or oral corticosteroid-dependent disease; anti-IL-4Rα therapy when FeNO-high Type 2 inflammation and major atopic comorbidities are present; and anti-TSLP therapy when the phenotype is mixed or biomarker-low yet remains uncontrolled.[1-4,12]

The best biologic is not simply the newest or broadest agent, but the one that most closely matches the patient's dominant biology, exacerbation burden, corticosteroid burden, and comorbidity profile. Reassessment after initiation remains essential, because an effective biologic strategy depends not only on selecting the right first agent, but also on recognizing when switching is needed to achieve better control, reduce severe exacerbations, minimize systemic corticosteroid toxicity, and support truly individualized care.[1-4,9]

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