Step Therapy in Asthma: When and How to Step Up or Down

Pediatric and Adult Patients — An Evidence-Based Medicine Review

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Learning Objectives

01 Apply GINA 24/25/26, NAEPP EPR-4, BTS/SIGN, and AAAAI/ACAAI guideline frameworks to step-based asthma management.

02 Identify clinical criteria for stepping UP therapy, including uncontrolled symptoms, exacerbation risk, and biomarker thresholds.

03 Define evidence-based criteria for stepping DOWN therapy safely, including 3-month control requirement and ICS reduction strategies.

04 Differentiate pediatric vs. adult step-therapy thresholds, including age-specific MART/SMART eligibility and biologic indications.

05 Evaluate the role of FeNO, blood eosinophils, and phenotyping in personalizing step therapy decisions.

SECTION 1

Stepwise Framework: Guideline Landscape

GINA 2026 · NAEPP EPR-4 2020 · BTS/NICE/SIGN · AAAAI/ACAAI

Major Guideline Frameworks: Key Differences & Consensus

GINA 24/25/26 (Global)

Two tracks (Track 1 preferred: ICS-formoterol reliever). All patients (including EIB) must receive ICS-containing therapy. SABA-alone is no longer recommended.

Climate/extreme weather and >10% increase in FEV1

NAEPP EPR-4 2020 (USA)

Six-step framework. SMART recommended from Step 3. ICS+LABA preferred over ICS+LAMA at Step 3–4. Triple therapy (ICS/LABA/LAMA) = preferred Step 5

Allergen Immunotherapy

BTS/SIGN/NICE 19/24/25

Five-step model. ICS cornerstone from Step 2. LABA added at Step 3. Specialist review before Step 4–5 escalation

Parallels GINA guidelines

AAAAI/ACAAI Asthma Yardstick

Sustained step-up requires ruling out non-adherence, poor technique, environmental triggers, and comorbidities BEFORE escalating pharmacotherapy

GINA 24/25/26 Report | NAEPP EPR-4 (2020) PMID: 33278043 | BTS/SIGN 2019 | Chipps et al. Ann Allergy Asthma Immunol. 2017;118(2):133. PMID: 28153079

GINA 24/25/26 Step Therapy: Adults & Adolescents (≥12 yrs) — TRACK 1 (Preferred)

Step 1	Step 2	Step 3	Step 4	Step 5
As-needed low-dose ICS-formoterol	As-needed low-dose ICS-formoterol OR daily low-dose ICS + SABA prn	Low-dose ICS-formoterol MART (daily + as-needed)	Medium-dose ICS-formoterol MART	High-dose ICS-LABA + LAMA ± Biologic (phenotype-directed)
Mild, infrequent sx (<2×/wk)	*Symptoms >2×/month*	*Moderate; not controlled on Step 2*	*Persistently uncontrolled*	*Severe/refractory*

SECTION 2

When & How to Step UP

Clinical triggers, biomarkers, and evidence for escalation

SLIDE OBJECTIVE

Step-Up: Clinical Triggers & Pre-Step Checklist

KEY POINTS

- Step up only after ruling out non-adherence, poor technique, and triggers.
- Uncontrolled asthma ≥3 months despite current step warrants escalation.

SUPPORTING EVIDENCE

PRE-STEP CHECKLIST (GINA 24/25/26 / AAAAI Yardstick):
Before ANY step-up, confirm:

- ✔ Inhaler adherence assessed (>80% of doses taken)
- ✔ Inhaler technique verified and corrected
- ✔ Modifiable environmental triggers identified
- ✔ Comorbidities treated (rhinitis, GERD, obesity, OSA)
- ✔ Asthma diagnosis confirmed (spirometry, reversibility, FeNO)

CLINICAL TRIGGERS FOR STEP-UP:

- Daytime sx >2 days/week OR nighttime waking ≥1×/month
- SABA use >2 days/week (not for EIB prevention)
- Any activity limitation due to asthma
- FEV_1 <80% predicted; or ≥1 exacerbation requiring OCS in prior year

Chipps BE et al. Ann Allergy Asthma Immunol. 2017;118(2):133. PMID: 28153079 | GINA 24/25/26 Strategy Report, pp. 53–78

SLIDE OBJECTIVE

MART/SMART Therapy: The Cornerstone of Modern Step-Up

KEY POINTS

- MART reduces severe exacerbations by 40–64% vs. SABA alone or fixed-dose ICS+SABA.
- Network meta-analysis confirms SMART superiority for mild-to-moderate asthma (Steps 3–4).

SUPPORTING EVIDENCE

PICO — SYGMA 1 & 2 (O'Byrne et al., NEJM 2018):
P: Adults with mild asthma (N=8,000+ combined)
I: As-needed budesonide-formoterol (200/6 µg)
C: Twice-daily budesonide 200µg OR terbutaline prn
O: SYGMA 1: 64% reduction in severe exacerbations vs. terbutaline alone
SYGMA 2: Non-inferior to daily budesonide for exacerbations; 17% lower ICS exposure

Network Meta-Analysis — Terzano et al. ERJ 2020:
P: Adults, mild-to-moderate asthma (21 RCTs, N=32,096)
I: Low-dose SMART / as-needed ICS-LABA
C: Other as-needed regimens (SABA, ICS, LABA)
O: SMART significantly superior (RR <0.78; p<0.05) in reducing severe exacerbation risk

No significant difference in serious adverse events across strategies

O'Byrne PM et al. NEJM 2018;378(20):1865. PMID: 29768147 | Terzano C et al. Eur Respir J. 2020;56(3):2000625. PMID: 32430423

SLIDE OBJECTIVE

Step 3–4: Adding LABA to ICS — Network Meta-Analysis Evidence

KEY POINTS

- ICS+LABA reduces severe exacerbations and improves FEV_1 vs. ICS alone at Steps 3–4.
- Triple therapy (ICS/LABA/LAMA) provides further modest benefit at Step 4–5.

SUPPORTING EVIDENCE

Network Meta-Analysis — Yamasaki et al. Heliyon 2024:
P: Adults with asthma (56 RCTs, N=not reported)
I: ICS/LABA, ICS/LABA-SMART, triple therapy (ICS/LABA/LAMA)
C: ICS monotherapy
O: ICS/LABA-SMART had greatest reduction in severe exacerbation annualized rate

Triple therapy (ICS/LABA/LAMA) provided additional but modest benefit

NAEPP EPR-4 2020 — ICS+LABA vs. ICS+LAMA (Step 3):
P: Patients ≥12 years not controlled on ICS alone
I: Add LABA to ICS (Step 3 preferred)
C: Add LAMA to ICS
O: Conditional recommendation FAVORING ICS+LABA over ICS+LAMA (moderate certainty)

LAMA acceptable if LABA contraindicated or not tolerated

GINA 24/25/26: Add LAMA to medium/high-dose ICS-LABA only when persistently uncontrolled — modest FEV_1 improvement, limited effect on symptoms

Yamasaki A et al. Heliyon. 2024;10:e31186. PMC11252599 | NAEPP EPR-4, 2020. PMID: 33278043 | GINA 24/25/26, pp. 77–93

SLIDE OBJECTIVE

Biomarker-Guided Step-Up: FeNO, Eosinophils & T2 Inflammation

KEY POINTS

- FeNO ≥25 ppb (adults) identifies Type-2 inflammation; predicts ICS responsiveness.
- Blood eosinophils ≥300 cells/µL + high FeNO confer highest exacerbation risk.

SUPPORTING EVIDENCE

ATS Clinical Practice Guideline — FeNO (Dweik et al., updated to Couillard 2022):
P: Adults and children ≥5 yrs with asthma or suspected asthma
I: FeNO-guided therapy decisions (step-up if FeNO >25 ppb)
C: Symptom-guided care
O: FeNO-guided care: RR 0.73 (95% CI 0.62–0.86) for exacerbations; RR 0.79 for OCS use

Modest improvement in FEV_1 (MD 1.11%; 95% CI 0.02–2.21%)

Biomarker Combination — Pediatric Evidence (Frontiers in Allergy 2026):
P: Children with severe asthma
I: FeNO + blood eosinophils + IgE to guide ICS and biologic selection
C: Symptom-based escalation alone
O: Combined T2 biomarker strategy improves phenotyping accuracy; predicts biologic response

FeNO ≥25 ppb + eos ≥300: highest future exacerbation risk (post-hoc QUEST analysis)

Pitfalls: FeNO suppressed by ICS; elevated by eosinophilic rhinitis; not recommended age <4 yrs

ATS FeNO Guideline, AJRCCM 2011. PMID: 21680878 | Frontiers Allergy 2026;6:1757445 | NAEPP EPR-4 2020. PMID: 33278043

SECTION 3

When & How to Step DOWN

Safety, timing, and evidence for de-escalation

SLIDE OBJECTIVE

Step-Down: When Is It Safe to De-escalate?

KEY POINTS

- Step down only after ≥3 months of sustained well-controlled asthma.
- Reduce ICS dose 25–50% every 3 months; reassess at each step.

SUPPORTING EVIDENCE

GINA 24/25/26 Criteria for Considering Step-Down:

- ✔ Asthma well-controlled for ≥3 consecutive months
- ✔ No exacerbations or OCS courses in past year
- ✔ FEV_1 ≥80% predicted (or baseline)
- ✔ Low exacerbation risk factors confirmed
- ✔ Preferred first step: reduce ICS dose by 25–50%
- ✔ Do NOT withdraw ICS completely unless diagnosis is re-evaluated

Strategy: At Step 4 (ICS-LABA), reduce ICS first before removing LABA

Cochrane Review — Crossingham et al. 2017 (ICS Dose Reduction):
P: Adults with well-controlled asthma (6 RCTs, N=1,654)
I: 50–60% ICS dose reduction
C: Continued fixed-dose ICS
O: No statistically significant difference in exacerbations, symptoms, or lung function
Evidence quality: LOW to VERY LOW (risk of bias, imprecision)

Authors: "Insufficient evidence to confirm net benefit or harm of stepping down ICS"

Duration: 12–52 weeks; additional well-designed RCTs needed

SLIDE OBJECTIVE

Step-Down to As-Needed ICS/FABA: New Meta-Analytic Evidence (2025)

KEY POINTS

- Stepping down to as-needed ICS/formoterol shows comparable outcomes to scheduled ICS + SABA.
- Cumulative ICS dose is significantly lower with as-needed regimens (high certainty).

SUPPORTING EVIDENCE

Systematic Review & Meta-Analysis — Rank et al. JACI: In Practice 2025:
P: Adults with stable asthma on scheduled ICS + as-needed FABA (7 RCTs; N=2,485)
I: Step down to as-needed ICS/FABA (ICS-formoterol or ICS-albuterol)
C: Continue scheduled ICS + as-needed FABA
O: Severe exacerbations: RR 0.88 (95% CI 0.67–1.17) — no significant difference
Asthma QoL: MD −0.11 (95% CI −0.28 to 0.07) — no significant difference
Lung function (FEV_1): comparable between groups
Cumulative ICS dose: SIGNIFICANTLY LOWER with as-needed regimen

Clinical Implications:

- Step-down to as-needed ICS/FABA is a valid strategy for stable, well-controlled patients
- Supports GINA Track 1 as a downward step, not just an upward one
- Reduces cumulative steroid burden — particularly relevant for children & long-term users
- Shared decision making essential: patient preference, adherence patterns, exacerbation history

Rank MA et al. J Allergy Clin Immunol Pract. 2025. DOI: 10.1016/j.jaip.2025.06.028

SLIDE OBJECTIVE

ICS Dose Reduction vs. LTRA Discontinuation: Step-Down at GINA Step 4

KEY POINTS

- ICS dose reduction (vs. stopping montelukast) associated with fewer treatment failures at 3 months.
- GINA 24/25/26 aligns: at Step 4, reduce ICS first, continue second controller.

SUPPORTING EVIDENCE

Pilot RCT — BMC Pulmonary Medicine 2025:
P: Adults with well-controlled asthma on medium/high-dose ICS-LABA + montelukast (GINA Step 4; N=73)
I: Group A — ICS dose reduction (n=37)
C: Group B — Montelukast discontinuation (n=36)
O: ACT score: No significant difference between groups (p=0.123)
Treatment failures at 3 months: 0 (Group A) vs. 5 (Group B) — p=0.01

Conclusion: ICS dose reduction preferred as first step-down strategy in Step 4 patients

GINA 24/25/26 Guidance on LTRA:

- Montelukast may be continued when stepping down ICS dose
- FDA Black Box Warning: neuropsychiatric effects — perform benefit-risk discussion before initiating
- 2023 systematic review: no direct association with suicide/depression events, but individual risk varies
- NOT recommended as first-line add-on for most patients

BMC Pulm Med. 2025;25(1). PMC11980050 | GINA 2024, Chapter 4 | FDA Montelukast Boxed Warning (2020)

SECTION 4

Pediatric Step Therapy: Age-Specific Considerations

Children <5 yrs · 6–11 yrs · Adolescents

Pediatric Step Therapy: Age-Stratified GINA 24/25/26 & NAEPP EPR-4 2020

Children <5 years (GINA 24/25/26)

Step 1: PRN SABA. Step 2: Low-dose ICS daily or LTRA. Step 3: Double low-dose ICS or ICS+LTRA. Step 4: Moderate ICS±LABA (age ≥4). NO LAMA in this age group.

Children 6–11 years (GINA/EPR-4)

Step 1: Low-dose ICS when SABA used (GINA) or PRN SABA (EPR-4). MART preferred from Step 3 (age ≥4). Medium-dose ICS-LABA at Step 4 for daily sx + low FEV_1.

ICS & Growth — Key Evidence

Concerns about growth suppression primarily with HIGH doses / prolonged use. Standard maintenance ICS: minor, partially reversible effect. Benefit-risk strongly favors ICS over uncontrolled asthma.

Adherence in Pediatrics

Mean ICS adherence in school-age children: 36.2% (UK primary care study, N=130). Only 14.6% had good adherence (≥75%). ALWAYS assess adherence before step-up in children.

GINA 2024 | NAEPP EPR-4 2020 (PMID: 33278043) | Pediatr Drugs 2025 | Asthma adherence: PMC10039953

SLIDE OBJECTIVE

Children <5 Yrs with Viral-Triggered Wheezing: Intermittent ICS Strategy

KEY POINTS

- Short-course ICS (7–10 days) at URTI onset reduces wheezing exacerbations in at-risk toddlers.
- NAEPP EPR-4 (2020): Conditional recommendation with moderate evidence for short-course ICS in ≥3 wheezing episodes.

SUPPORTING EVIDENCE

NAEPP EPR-4 2020 — Intermittent ICS in Children 0–4 yrs:
P: Children 0–4 yrs with ≥3 viral-triggered wheezing episodes in lifetime OR ≥2 in past year; asymptomatic between episodes
I: Short-course ICS (7–10 days) + as-needed SABA at URTI onset
C: As-needed SABA alone
O: Conditional recommendation; moderate certainty of evidence
Reduces severe wheezing episodes requiring OCS or hospitalization
NOT recommended for continuous daily ICS at Step 1 in this age group

GINA 24/25/26 Alignment:

- Step 2 (age <5): Low-dose daily ICS OR daily LTRA preferred if persistent symptoms
- Episodic ICS at URTI onset: one of multiple accepted options
- FeNO NOT recommended for guiding step changes in children <4 years
- Distinguishing recurrent viral wheeze from early atopic asthma is key — API score assists

Key distinction: Viral-triggered episodic wheeze (preschool) ≠ persistent allergic asthma

NAEPP EPR-4 2020. PMID: 33278043 | GINA 2024 Children <5 yrs Framework, pp. 159–175

SECTION 5

Biologic Step-Up Therapy: Severe Asthma (Step 5)

Phenotyping · Target selection · Stepping down biologics

Biologic Therapy at Step 5: Phenotype-Directed Selection (GINA 24/25/26 / EAACI)

Biologic	Target	Key Biomarker / Indication	Min. Age	Exacerbation ↓
Omalizumab	Anti-IgE	Allergic phenotype, elevated total IgE, skin test+	≥6 yrs	38%-58%
Mepolizumab	Anti-IL-5	Eos ≥150 at Tx start or ≥300 in past year; ≥2 OCS courses	≥6 yrs	47%-53% CT / 71%-81% RW
Benralizumab	Anti-IL-5Rα	Eos ≥300; ≥2 exacerbations/year on high-dose ICS-LABA	≥12 yrs	50% CT / 45%-80% RW
Dupilumab	Anti-IL-4Rα	T2 inflammation (eos or FeNO); OCS-dependent asthma	≥6 yrs	47%-71%
Tezepelumab	Anti-TSLP	Severe uncontrolled asthma (any T2 biomarker level)	≥12 yrs	56%-71%

Giavina-Bianchi P et al. Curr Opin Allergy Clin Immunol. 2021. PMC8362167 | Agache I et al. Allergy. 2020;75:1080. PMID: 32034960 (EAACI) | GINA 2024 Severe Asthma Guide

Biologic Therapy at Step 5: Phenotype-Directed Selection (GINA 24/25/26 / EAACI)

Biologic	Target	Key Biomarker / Indication	Min. Age	Exacerbation ↓
Depemokimab	Anti-IL-5	Eos ≥150 at Tx start or ≥300 in past year; ≥2 OCS courses	≥12 yrs	48%-58%
Reslizumab	Anti-IL-5	Eos ≥400; ≥2 OCS courses	≥18 yrs	50%-60%

Giavina-Bianchi P et al. Curr Opin Allergy Clin Immunol. 2021. PMC8362167 | Agache I et al. Allergy. 2020;75:1080. PMID: 32034960 (EAACI) | GINA 2024 Severe Asthma Guide

SLIDE OBJECTIVE

Stepping Down Biologics: Growing Evidence, Limited Consensus

KEY POINTS

- Most biologic-treated severe asthma patients can achieve clinical remission within 12 months.
- Step-down after biologic response is feasible; evidence base is growing but not yet definitive.

SUPPORTING EVIDENCE

Retrospective Study — Severe Asthma Biologic Remission:
P: Adults with severe asthma treated with omalizumab, benralizumab, or dupilumab (N=48; 2020–2025)
I: Biologic therapy for 12 months
O: 75% achieved clinical remission (ACT, exacerbation frequency, OCS use, FEV_1)
75% achieved biological remission (FeNO, eosinophil levels)
All three agents achieved comparable remission rates at 12 months

GINA 24/25/26 Guidance on Stepping Down Biologics:

- No definitive duration of biologic therapy established
- For patients with GOOD response: re-evaluate after 12 months — consider dose-interval extension
- Step-down should include: reduction of background OCS first, then ICS dose
- Structured stopping rules: clinical remission sustained ≥12 months → discuss discontinuation trial
- Expert consensus: do NOT stop biologic without specialist review; relapse risk real

Recent Evidence: Systematic review confirms limited consensus on biologic stopping criteria

PMC12300431 (2025) | Kyriakopoulos C et al. Eur Respir Rev. 2024;33:230238 | GINA Severe Asthma Guide 24/25/26, pp. 46–50

SECTION 6

Clinical Bottom Line & Areas of Uncertainty

Practice pearls and evidence gaps for 2026 and beyond

Clinical Bottom Line

STEP UP:	Rule out non-adherence, poor technique, and comorbidities FIRST. Use ACT <19 or AIRQ >1 as objective triggers. Add FeNO + eosinophils for phenotype-informed escalation.
STEP DOWN:	Require ≥3 months sustained control before de-escalating. Reduce ICS dose 25–50% as first maneuver. As-needed ICS/FABA is a safe, ICS-sparing alternative in stable patients (Rank et al. 2025).
MART/SMART:	ICS-formoterol as maintenance AND reliever is the cornerstone of GINA 2024 Track 1 (Steps 1–4). It reduces severe exacerbations by 40–64% vs. SABA alone. Preferred for patients ≥4 years.
BIOLOGICS:	Reserve for GINA Step 5 with confirmed T2 phenotype despite high-dose ICS-LABA. All 7 FDA-approved biologics significantly reduce exacerbation rate (IRR 0.43–0.56). Match biologic to dominant biomarker.
PEDIATRICS:	Age-specific pathways critical. LABA not recommended <4 yrs. Address adherence (mean 36% in school-age children). Growth monitoring essential. FeNO not validated <4 yrs.

Areas of Uncertainty & Active Research Questions (2026)

Step-Down Evidence Gap

Cochrane 2017: Low-to-very-low quality evidence for ICS dose reduction. Larger, longer RCTs needed. Optimal step-down timing and pace remain undefined.

Biologic Stopping Rules

No validated criteria for biologic discontinuation. 'Remission' definition not standardized. Head-to-head biologic comparisons limited. Duration of therapy unknown.

Pediatric Biologic Evidence

Biologic recommendations for children largely extrapolated from adult RCTs. Age-specific biomarker thresholds, dosing, and stopping rules need prospective pediatric trials.

T2-Low / Non-Eosinophilic Asthma

Limited effective therapies. Mechanisms and new targets (anti-IL-33, anti-TSLP) under investigation.

Crossingham I et al. Cochrane 2017. CD011802 | Kyriakopoulos C et al. Eur Respir Rev. 2024;33:230238 | Frontiers Allergy 2026 | GINA 2024

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