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Chapter 23

Primary-Care-Forward Asthma Management: Evolving Reliever Paradigms and Stewardship from the 2019 Landmark to GINA 2024–2026

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Abstract

The Global Initiative for Asthma (GINA) strategy reports have undergone critical updates between 2024 and 2026, marking a complete transition from symptom-based bronchodilator rescue to proactive, anti-inflammatory-driven asthma control [1-3]. This report provides a comparative clinical analysis of the GINA 2024, GINA 2025, and GINA 2026 updates, detailing the structural evolution of treatment tracks, advancements in diagnostic criteria, and the integration of novel therapeutics [4-6]. While GINA 2024 established the preferred Track 1 (ICS-formoterol) and alternative Track 2 (SABA reliever) frameworks to mitigate SABA overuse [1]. GINA 2025 integrated Type 2 biomarkers (FeNO and blood eosinophils) and age-specific diagnostic pathways for pediatric populations aged 5 years and under [2, 7-9]. GINA 2026 represents a landmark primary-care-forward update, dismantling SABA monotherapy at Step 1 of Track 2 by introducing combination ICS-SABA as an alternative anti-inflammatory reliever (AIR) [3]. Additionally, GINA 2026 elevates oral corticosteroid (OCS) stewardship as a formal priority, mandates device consistency, and incorporates the twice-yearly anti-IL-5 biologic depemokimab for severe eosinophilic asthma [3, 6, 10, 11]. This systematic analysis serves as an essential resource for clinicians navigating these evolving therapeutic paradigms to optimize patient-centered asthma care globally.

Keywords: Asthma, GINA Guidelines, Inhaled Corticosteroids (ICS), Short-Acting Beta2-Agonists (SABA), Anti-Inflammatory Reliever (AIR), Maintenance and Reliever Therapy (MART), Biologics, Depemokimab, Corticosteroid Stewardship.

1. Introduction

Asthma remains a highly prevalent, heterogeneous chronic respiratory disease that affects more than 260 million people globally and is responsible for over 450,000 deaths annually, the vast majority of which are clinically preventable [4]. The Global Initiative for Asthma (GINA) was established in 1993 in collaboration with the World Health Organization (WHO) and the National Heart, Lung, and Blood Institute (NHLBI) to reduce asthma-associated morbidity and mortality by systematically translating evolving scientific evidence into actionable clinical recommendations [12].

For decades, short-acting beta2-agonist (SABA) bronchodilators served as the baseline rescue therapy for acute symptoms [1]; however, clinical trials and epidemiological data eventually revealed that SABA monotherapy down-regulates beta-receptors, induces rebound airway hyper-responsiveness, masks progressive mucosal inflammation, and significantly raises the risk of severe, life-threatening exacerbations [1, 2]. This critical safety concern prompted a landmark clinical paradigm shift in 2019, when GINA recommended that all adults and adolescents receive inhaled corticosteroid (ICS)-containing anti-inflammatory therapy to establish basic safety, initiating the transition toward the contemporary anti-inflammatory reliever (AIR) model [2, 13].

From 2024 to 2026, the GINA strategy reports have steadily refined and expanded this safety-first paradigm [1-3]. While the GINA 2024 update established distinct treatment Tracks for adults and adolescents to categorize preferred (Track 1, ICS-formoterol) and alternative (Track 2, SABA) reliever strategies [1], GINA 2025 heavily integrated Type 2 inflammatory biomarkers (including blood eosinophils

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and fractional exhaled nitric oxide) alongside explicit diagnostic pathways for young children [2]. The GINA 2026 update represents a landmark primary-care-forward evolution, completely eliminating SABA monotherapy at the first step of the alternative track by introducing combination ICS-SABA as an as-needed reliever [3]. By evaluating the structural, pharmacological, and operational updates spanning GINA 2024, GINA 2025, and GINA 2026, this clinical report outlines a comprehensive roadmap for contemporary clinical practice, patient safety, and global corticosteroid stewardship.

Evolution of the Anti-Inflammatory Reliever Strategy and Treatment Tracks

The Global Initiative for Asthma (GINA) has steadily reformed the clinical approach to asthma, shifting the therapeutic goal from temporary bronchodilation to proactive, anti-inflammatory control [1-3]. Prior to this 2019 shift, mild asthma was treated purely with symptom-driven SABA bronchodilators, a practice that heavily contributed to preventable mortality by leaving mucosal inflammation unmanaged. The 2019 update established that a micro-dose of anti-inflammatory controller must accompany every instance of rescue bronchodilation [13]. In 2024, this paradigm was structured around two major treatment tracks [1]. Track 1, designated as the preferred therapeutic pathway, relies on an anti-inflammatory reliever (combination low-dose inhaled corticosteroid and formoterol, such as budesonide-formoterol) used as needed at all steps, transitioning into maintenance and reliever therapy (MART) at Steps 3 and 4 [1]. The clinical basis for this preference is rooted in the rapid onset of formoterol and the protective anti-inflammatory cover of the inhaled corticosteroid (ICS) [4]. Utilizing an anti-inflammatory reliever reduces severe exacerbations by approximately 60% to 65%, lowers oral corticosteroid requirements, and decreases urgent healthcare utilization compared to short-acting beta2-agonist (SABA) reliever regimens [3].

Table 1: Comprehensive Table of Differences Across GINA 2024, GINA 2025, and GINA 2026 Guidelines [1-3]

Clinical Dimension	GINA 2024 Update [1]	GINA 2025 Update [2]	GINA 2026 Update [3]
Primary Clinical Focus	Structural track-based classification and SABA avoidance.	Characterization of clinical phenotypes and biomarker-driven diagnosis.	Primary-care operationalization, OCS stewardship, and point-of-care implementation.
Preferred Reliever (Track 1)	As-needed combination low-dose ICS-formoterol (budesonide-formoterol 80/4.5 mcg or 160/4.5 mcg).	Reinforces ICS-formoterol (AIR) as the preferred reliever across all asthma severities.	Reaffirms Track 1 (ICS-formoterol) as the preferred clinical strategy.
Alternative Reliever (Track 2)	SABA as reliever across all steps. Low-dose ICS taken with SABA at Step 1.	Maintains SABA reliever alongside regular controller. Tracks SABA overuse (($\geq$3 canisters/year).	Adds combination ICS-SABA as an as-needed reliever at Step 1, providing a second AIR option.
Diagnostic Approach & Resources	Spirometry is preferred; Peak Expiratory Flow (PEF) is emphasized as an alternative for low-resource clinics.	Integrates Type 2 biomarkers (FeNO and blood eosinophils) to support diagnosis if lung function is normal.	Standardizes objective exacerbation assessment (e.g., PRAM) and screens for urgent escalation factors.
Step 5 Triple-Therapy Step-Up	Add-on long-acting muscarinic antagonists (LAMA) and phenotype assessment.	Focuses on optimizing Step 5 care using LAMA, azithromycin, or phenotype-specific biologics.	Endorses budesonide-formoterol-glycopyrronium triple combination alongside fluticasone-based options.
Severe Asthma Biologics	Standard biologics recommended based on clinical and inflammatory phenotypes.	Outlines a highly specific, biomarker-driven selection algorithm matching phenotypes with biologics.	Incorporates Depemokimab, a twice-yearly (every 26 weeks) anti-IL-5 biologic. References biosimilar anti-IgE.
Pediatric Management ($\leq$ 5 years)	Trial of daily low-dose ICS for frequent symptoms; SABA reliever; no ICS-LABA.	Introduces a 3-criterion diagnostic pathway. Resolves nebulized salbutamol dosing error.	Maintains 2025 diagnostic criteria, reserves daily ICS for children with frequent interval symptoms or severe exacerbations, and introduces primary-care acute flowcharts.
Corticosteroid Stewardship	Focuses on preventing severe exacerbations requiring systemic steroids.	Highlights risks of unmanaged inflammation and unchecked exacerbations.	Establishes Oral Corticosteroid (OCS) stewardship as a formal priority, tracking cumulative exposure.
Device Consistency & Delivery	Emphasizes proper inhaler technique and action plans.	Stresses regular technique reviews and shared decision-making for choosing devices.	Recommends prescribing a single device class per patient. Mandates shaking suspension MDIs and waiting 30 seconds.

Track 2 represents an alternative clinical approach, relying on SABA as the reliever, which requires patients to take a separate daily maintenance controller [1]. However, clinical evidence increasingly highlights the risks associated with SABA monotherapy. Regular SABA use for as short as one to two weeks causes significant down-regulation of beta2-receptors, diminishes bronchoprotective efficacy, and triggers rebound hyper-responsiveness [1]. Overusing SABAs masks the underlying progression of chronic airway inflammation and is associated with poor clinical outcomes; dispensing three or more SABA canisters annually is linked to a heightened risk of severe exacerbations, while dispensing twelve or more annually elevates the risk of asthma-related mortality [4].

In GINA 2026, the SABA monotherapy reliever paradigm is further dismantled [3]. While Track 1 remains the preferred path, Track 2

has been updated to include a combination ICS-SABA as-needed reliever at Step 1 [3]. This update formally adds a second anti-inflammatory reliever (AIR) option, ensuring that even patients on an alternative track receive anti-inflammatory protection with every rescue dose, and rendering SABA-alone relief obsolete at the entry step of treatment [3].

Evolving Diagnostic Paradigms and Inflammatory Phenotyping

The diagnostic approach across the three strategy updates transitioned from basic physiological measurements to a multidimensional evaluation integrating lung function, Type 2 inflammatory biomarkers, and age-specific clinical criteria [1-3]. In 2024, GINA addressed global diagnostic challenges by revising its clinical flowchart. While spirometry remains the gold standard, peak expiratory flow (PEF) was emphasized as a viable alternative for early diagnosis in resource-limited environments [1].

In 2025, GINA refined the diagnostic framework by integrating Type 2 biomarkers [2]. In patients presenting with typical symptoms but normal or unavailable lung function tests, elevated fractional exhaled nitric oxide (FeNO $\geq$ 20 to 35 ppb) or blood eosinophil counts ($\geq$ 150 to 300 cells/μL) were formally recognized as supportive of a Type 2-high allergic or eosinophilic phenotype [2]. However, clinicians are reminded that low biomarker levels do not exclude asthma, and elevated levels can occur in non-asthma conditions [2].
Furthermore, GINA 2025 introduced clinical phenotypes to guide patient-centered care [2]:

- **Allergic Asthma**: Typically beginning in childhood and associated with personal or family histories of atopic diseases, responding well to inhaled corticosteroids.
- **Nonallergic Asthma**: Presenting with neutrophilic, eosinophilic, or pauci-granulocytic sputum profiles, tending to be less responsive to standard corticosteroid therapy.
- **Cough-Variant Asthma**: Characterized by cough as the sole symptom, with variable airflow limitation often demonstrated only during bronchial provocation testing.
- **Adult-Onset Asthma**: Occurring more frequently in women, often nonallergic and relatively refractory to inhaled corticosteroids, requiring a thorough clinical evaluation to rule out occupational exposures.
- **Asthma with Persistent Airflow Limitation**: Resulting from structural airway remodeling over time.
- **Asthma with Obesity**: Characterized by prominent respiratory symptoms and a distinct pattern of airway inflammation with minimal eosinophilic involvement, making it relatively resistant to standard anti-inflammatory therapies.

For pediatric populations, GINA 2025 established a pragmatic 3-criterion diagnostic pathway for children aged 5 years and under [2,9]. Confirming asthma in this age group is challenging due to the difficulty of performing objective spirometry [2]. Under this framework, a diagnosis requires meeting three criteria: a history of variable respiratory symptoms (dry cough, wheeze worse at night or triggered by laughter/exertion), clinical signs of lower airway obstruction (accessory muscle use, prolonged expiration, decreased air exchange), and a documented response to an 8-to-12-week trial of controller therapy [2]. To correct a critical dosing error in pediatric acute care, a minor update in November 2025 revised the nebulized salbutamol dose for children under 5 from 0.25 mg to 2.5 mg [10].

By 2026, the clinical emphasis transitioned to point-of-care risk stratification [3]. Subjective clinical assessments were replaced by standardized objective scoring systems, such as the Pediatric Respiratory Assessment Measure (PRAM) in pediatric populations [3]. Additionally, GINA 2026 mandated that primary care providers screen for high-risk clinical features during every clinical visit [3]. This screening involves identifying patients with a history of mechanical ventilation, recent hospitalizations, multiple emergency department visits, current or recently discontinued oral corticosteroid courses, food allergies, or poor treatment adherence [3].

Advances in Step 5 Therapeutics: Triple-Combination Options and Biologics

For patients with severe, uncontrolled asthma at Step 5, the therapeutic options evolved from basic phenotype assessments to a structured, biomarker-driven biologic matching algorithm, alongside expanded triple-therapy options [1-3].

In 2024, Step 5 interventions relied primarily on add-on long-acting muscarinic antagonists (LAMA), tiotropium, and phenotypic assessments to guide the initiation of biologics such as benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab, and Tezepelumab [1].

In GINA 2025, a highly specific biologic selection algorithm was introduced for severe, refractory Type 2-high and Type 2-low phenotypes [2,8]:

- **Type 2-High Allergic Asthma**: Defined by perennial sensitization and elevated total/specific IgE, omalizumab is recommended as first-line therapy.
- **Type 2-High Eosinophilic Asthma with Moderate Eosinophilia or Raised FeNO**: Dupilumab is preferred due to its dual blockade of the IL-4 and IL-13 pathways across different IgE strata.
- **Type 2-High Eosinophilic (Intrinsic/Late-Onset) Asthma**: Anti-IL-5 biologics, such as mepolizumab or benralizumab, are recommended first, with dupilumab or tezepelumab reserved for non-responders.
- **Type 2-Low Asthma**: Characterized by the absence of Type 2 biomarkers, tezepelumab is recommended due to its ability to target TSLP upstream in the inflammatory cascade.

To assess treatment efficacy, GINA 2025 established a 16-to-24-week trial period, requiring a minimum 50% reduction in severe exacerbations, a drop in FeNO of $\geq$ 10 ppb, or an FEV1 gain of $\geq$ 0.1 L to continue biologic therapy [2].

In 2026, the Step 5 toolkit was expanded to include a new triple-combination option: budesonide-formoterol-glycopyrronium [3]. This provides primary care clinicians with greater pre-biologic flexibility alongside existing fluticasone-based triple combinations. GINA 2026 also incorporated depemokimab, the first ultra-long-acting anti-IL-5 monoclonal antibody approved in December 2025 [3, 6]. Dosed every 26 weeks (twice yearly), depemokimab targets severe eosinophilic asthma [3]. Data from the phase 3 SWIFT-1 and SWIFT-2 trials demonstrated a 50% reduction in annualized exacerbation rates compared to placebo [3,14]. In addition, the NIMBLE switch trial showed that patients stable on short-acting anti-IL-5 biologics (such as mepolizumab or benralizumab) could safely transition to twice-yearly depemokimab without loss of symptom control or lung function.6 To address cost barriers in resource-limited clinics, GINA 2026 also referenced biosimilar anti-IgE (omalizumab-igec) to expand access [3].

Steroid Stewardship, SABA Avoidance, and Practical Inhaler Optimization

The evolution of the guidelines reflects a systematic effort to reduce SABA reliance, minimize oral corticosteroid (OCS) toxicity, and optimize inhaler delivery techniques [1-3]. In 2024, GINA detailed the physiological mechanisms of SABA damage, noting that regular SABA use downregulates beta2-receptors, diminishes bronchoprotection, and causes rebound hyper-responsiveness [1]. Overuse of SABAs also masks worsening chronic airway inflammation, increasing the risk of severe exacerbations and asthma-related mortality [1,2].

In 2025, GINA addressed clinical prescription practices, recommending that healthcare providers track SABA prescriptions and identify patients ordering more than three canisters annually for clinical review [2,7]. Pharmacists and primary care providers were encouraged to invite flagged patients for reviews to evaluate their inhaler technique and adherence to anti-inflammatory therapies [2].

In GINA 2026, Oral Corticosteroid (OCS) stewardship was established as a formal priority [3]. Clinicians are directed to treat OCS as a last resort, utilizing minimum effective doses and durations, while actively tracking a patient's cumulative exposure [3]. This mandate is driven by the serious long-term systemic toxicities associated with repeated OCS courses, including type 2 diabetes, osteoporosis, and adrenal suppression [3].

To improve practical drug delivery, GINA 2026 introduced specific device and technique recommendations [3]:

- **Device Consistency**: To minimize "device confusion," clinicians are advised to prescribe a single device class (e.g., all pMDIs or all DPIs) per patient and minimize device switching.
- **Correct MDI Technique**: The 2026 report formalized a recommendation to shake metered-dose suspension inhalers before every single puff and wait 30 seconds between inhalations. This addresses clinical data showing that failing to shake suspension formulations dramatically alters the delivered drug dose, undermining therapeutic efficacy.
- **GLP-1 Receptor Agonist Data**: Recognizing obesity as a major non-eosinophilic comorbidity characterized by high symptom burdens and corticosteroid resistance, GINA 2026 highlighted early observational data suggesting that GLP-1 receptor agonists may improve asthma outcomes, identifying this as an area to watch.

Conclusions and Healthcare System Implications

The evolution of the GINA strategy reports from 2024 to 2026 represents a shift toward personalized, biomarker-driven, and primary-care-forward asthma management [1-3]. By providing primary care clinicians with structured flowcharts, expanded triple-therapy options, and objective assessment tools, GINA has made complex asthma management more accessible [3]. However, this shift requires clinical practitioners to develop a deeper understanding of device consistency, biomarker interpretation, and oral corticosteroid (OCS) stewardship [2,3].

Furthermore, GINA's complete transition away from SABA monotherapy highlights a significant global health disparity. In low- and middle-income countries, the high cost and limited availability of inhaled corticosteroids contribute to the fact that 96% of global asthma deaths occur in these regions [3]. GINA's 2026 World Asthma Day theme, "Access to anti-inflammatory inhalers for everyone with asthma – still an urgent need," emphasizes that clinical guidelines cannot improve global outcomes without corresponding policy, manufacturing, and regulatory changes to ensure affordable access to anti-inflammatory relievers [11].

Abbreviations

AIR: Anti-Inflammatory Reliever
APA: American Psychological Association
BEC: Blood Eosinophil Count
DPI: Dry-Powder Inhaler
EHR: Electronic Health Record
FDA: Food and Drug Administration (United States)
FeNO: Fractional Exhaled Nitric Oxide
FEV-1: Forced Expiratory Volume in 1 second
GERD: Gastroesophageal Reflux Disease
GINA: Global Initiative for Asthma
GLP-1: Glucagon-Like Peptide-1
ICS: Inhaled Corticosteroid
IgE: Immunoglobulin E
IL: Interleukin (e.g., IL-4, IL-5, IL-13)
IL-5R alpha: Interleukin-5 Receptor alpha
LABA: Long-Acting Beta 2 Agonist
LAMA: Long-Acting Muscarinic Antagonist
MART: Maintenance and Reliever Therapy
MDI: Metered-Dose Inhaler
NHLBI: National Heart, Lung, and Blood Institute
OCS: Oral Corticosteroid
PEF: Peak Expiratory Flow
pMDI: Pressurized Metered-Dose Inhaler
PRAM: Pediatric Respiratory Assessment Measure
SABA: Short-Acting Beta 2 Agonist
SMART: Symbicort Maintenance and Reliever Therapy
TSLP: Thymic Stromal Lymphopoietin
WHO: World Health Organization

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