Unravelling endotypes for treatment selection in severe type 2 asthma

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Agenda

What are the serious consequences of severe type 2 asthma?

How do endotyping and biomarkers guide treatment selection in severe type 2 asthma?

How do recent data and clinical guidelines inform the long-term management of patients with severe type 2 asthma?

What are the serious consequences of severe type 2 asthma?

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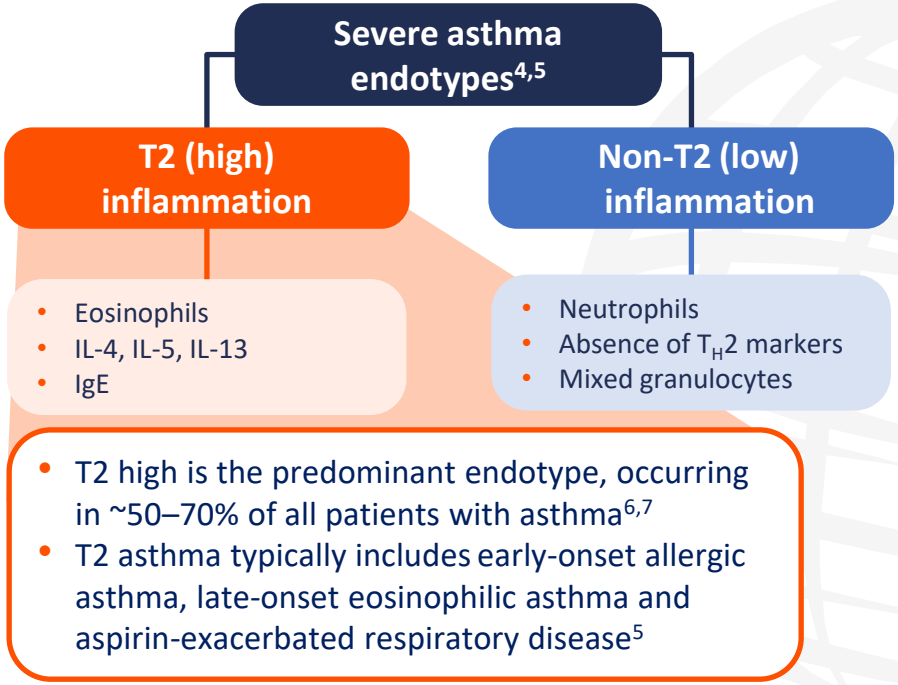
Severe asthma and its endotypes

- The **definition of severe asthma** used by ERS/ATS[1] and GINA[2] guidelines can be summarized as:

  Asthma that is uncontrolled despite good adherence with optimized use of high-dose ICS-LABA and treatment of contributory factors; or asthma that worsens when high-dose treatment is tapered down[2]

- Approximately 4–10% of patients with asthma have severe asthma[1,3]



ATS, American Thoracic Society; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta agonists; T2, type 2; T_H2, T helper 2 cells.

1. Chung KF, et al. *Eur Respir J*. 2014;43:343–73; 2. GINA. 2021. Available at: www.ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf (accessed 27 October 2021); 3. Hekking P-PW, et al. *J Allergy Clin Immunol*. 2015;135:896–902; 4. Godar M, et al. *MAbs.* 2018;10:34–45; 5. Kuruvilla ME, et al. *Clin Rev Allergy Immunol*. 2019;56:219–33; 6. Seys SF, et al. *Respir Res*. 2017;18:39; 7. Peters MC, et al. *J Allergy Clin Immunol*. 2014;133:388–94.

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The clinical and socioeconomic burden of severe asthma

Symptoms and physical functioning

- 89% report daily wheeze, 56% cough and 39% shortness of breath[1]
- Up to 94% report fatigue and poor sleep quality[1]
- 69% report physical activity limitations[1]
- Comorbidities more common in severe vs mild–moderate asthma[2]

Patient-reported social and economic burden

- Lower employment rates with severe vs mild asthma[2]
- Frequent job changes[2]
- 73% report decreased productivity in work[1]
- Significant social restrictions[3]

Treatment burden

- Can require self-management of a complex treatment regimen with multiple devices[1]
- Initial improvements in QoL with long-term OCS can be diminished by side effects[4]

Healthcare system burden

- Approx. 0.6–2.0 ED visits and 0.5–0.6 hospitalizations annually[2]
- Hospitalization costs >€10,000/patient/year[2]

ED, emergency department; OCS, oral corticosteroids; QoL, quality of life.

1. McDonald VM, et al. *Med J Aust*. 2018;209(Suppl. 2):S28–33; 2. Chen S, et al. *Curr Med Res Opin*. 2018;34:2075–88; 3. Foster JM, et al. *Eur Respir J*. 2017;50:1700765; 4. Volmer T, et al. *Eur Respir J*. 2018;52:1800703.

How do endotyping and biomarkers guide treatment selection in severe type 2 asthma?

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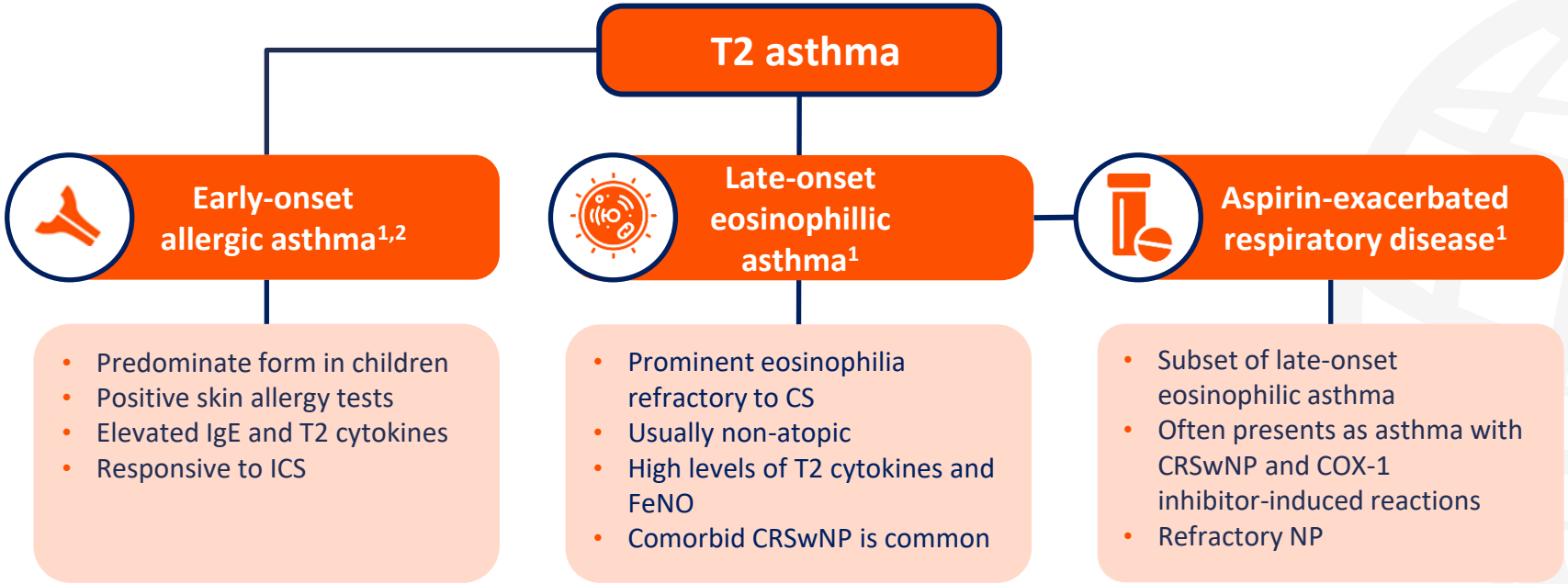
Phenotypes within the T2 asthma endotype



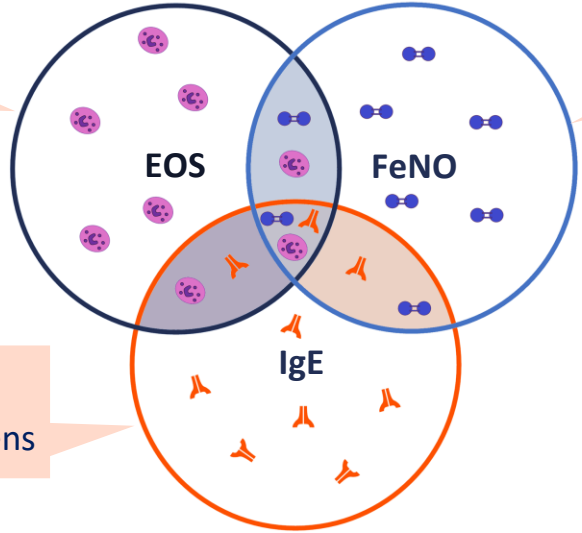
COX-1, cyclooxygenase-1; CRSwNP, chronic rhinosinusitis with nasal polyps; CS, corticosteroids; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; NP, nasal polyps; T2, type 2.

1. Kuruvilla ME, et al. *Clin Rev Allergy Immunol*. 2019;56:219–33; 2. Trivedi M, et al. *Front Pediatr*. 2019;7:256.

Biomarkers for T2 asthma[1–3]

T2 inflammation can be detected by individual or a combination of biomarkers

- Blood EOS ≥150/µL
- Sputum EOS ≥2%



- FeNO ≥20 ppb

- Skin-prick testing
- Specific IgE for relevant allergens

Biomarkers may need to be assessed **up to 3x, on the lowest possible OCS dose**

EOS, eosinophils; FeNO, fractional exhaled nitric acid; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; OCS, oral corticosteroid; ppb, parts per billion; T2, type 2.

1. GINA. 2021. Available at: www.ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf (accessed 27 October 2021);
2. Ray A, et al. *Am J Physiol Lung Cell Mol Physiol*. 2015;308:L130–40; 3. Brusselle GG, et al. *Nat Med.* 2013;19:977–9.

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Patient case

- 40-year-old female with severe asthma
- Currently on high-dose ICS
- Experiencing recurrent exacerbations and persistent symptoms
- No biomarker analysis/endotyping to date

What biomarker tests would you arrange for this patient, and how would the results inform your treatment choice?

ICS, inhaled corticosteroids.

How do recent data and clinical guidelines inform the long-term management of patients with severe type 2 asthma?

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Systematic approach to managing severe T2 asthma

- **International ERS/ATS guidelines** – recommendations for the management of severe asthma[1]
- **GINA 2021 Pocket Guide for Difficult-to-Treat & Severe Asthma** – summary for clinical practice[2]
- **EAACI Guidelines** – recommendations on the use of biologics[3]

Recommendations include:

- **Importance of assessment** of severe asthma phenotypes[2]
- **Consideration of targeted biologic treatment** for patients with severe asthma[3]
- **A decision tree** for assessing and treating severe asthma[2]

GINA 2021 Pocket Guide: Overall steps for the management of severe asthma[2]

1. **Investigate and manage** adults and adolescents with difficult-to-treat asthma
2. **Assess and treat** severe phenotypes
   Consider add-on non-biologic and add-on biologic T2-targeted treatments
3. **Monitor/manage** treatment

ATS, American Thoracic Society; EAACI, European Academy of Allergy and Clinical Immunology; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; T2, type 2.

1. Holguin F, et al. *Eur Respir J.* 2020;55:1900588; 2. GINA. 2021. Available at: www.ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf (accessed 27 October 2021); 3. Agache I, et al. *Allergy.* 2021;76:14–44.

Recent data with biologics in patients with severe asthma

Biologic	Indication[1]	Study details	Study population	Results
Benralizumab (anti-IL-5Rα)[2]	• Add-on, severe eosinophilic asthma	• PONENTE single-arm open-label trial (NCT03557307) • Steroid-reduction algorithm after benralizumab initiation	Adults with severe eosinophilic asthma on maintenance OCS	• 63% eliminated OCS; 82% eliminated OCS or achieved dosage ≤5 mg • 75% had no exacerbations during OCS reduction
Dupilumab (anti-IL-4Rα)[3]	• Add-on, severe/ OCS-dependent, eosinophilic/T2 asthma • CRSwNP	• TRAVERSE phase III OLE (NCT02134028)[4] • Long-term safety/efficacy	Patients from parent studies with moderate–severe or OCS-dependent severe asthma	• Safety/efficacy similar to parent studies • T2 inflammation subgroup results over 148 weeks: - AER decreased progressively - Lung function improvements sustained
Mepolizumab (anti-IL-5)[5]	• Add-on, severe eosinophilic asthma • EGPA	• REALITI-A observational cohort study • Effectiveness/safety	Patients with severe asthma	At 1-year follow-up: • 69% reduction in clinically significant exacerbations • 77% reduction in hospitalizations or ED visits
Itepekimab (anti-IL-33)[6]	• Investigational	• Phase II trial (NCT03387852) • Itepekimab vs itepekimab + dupilumab vs dupilumab vs PBO	Adults with moderate–severe asthma receiving ICS + LABA	• Itepekimab improved asthma control vs PBO • Itepekimab monotherapy: 22% lacked asthma control • Itepekimab + dupilumab : 27% lacked asthma control
Tezepelumab (anti-TSLP)[7]	• Investigational	• NAVIGATOR phase III trial (NCT03347279) • Efficacy/safety	Adults with severe, uncontrolled asthma	• Significant improvement in AER vs PBO plus SoC* at 1 year ($p<0.001$)

*SoC defined as medium- or high-dose inhaled corticosteroids plus at least one additional controller medication with or without OCS. AER, annualized exacerbation rate; CRSwNP, chronic rhinosinusitis with nasal polyps; ED, emergency department; EGPA, eosinophilic granulomatosis with polyangiitis; ICS, inhaled corticosteroids; IL, interleukin; LABA, long-acting beta agonists; OCS, oral corticosteroids; OLE, open-label extension; PBO, placebo; Rα, receptor alpha subunit; SoC, standard of care; T2, type 2; TSLP, thymic stromal lymphopoietin.

1. GINA. 2021. Available at: www.ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf (accessed 11 November 2021);
2. Menzies-Gow A, et al. *Lancet Respir Med*. 2021. doi: 10.1016/S2213-2600(21)00352-0; 3. Wechsler ME, et al. *Lancet Respir Med*. 2021. doi: 10.1016/S2213-2600(21)00322-2; 4. NCT02134028. Available at: www.clinicaltrials.gov/ct2/show/NCT02134028 (accessed 9 November 2021); 5. Harrison T, et al. *Eur Respir J*. 2020;56:2000151; 6. Wechsler ME, et al. *N Engl J Med*. 2021;385:1656–68; 7. Menzies-Gow A, et al. *N Engl J Med*. 2021;384:1800–9.

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Patient case

- 52-year-old male patient
- Currently managed with a biological therapy after prolonged treatment with conventional therapy
- Conventional therapy led to cumulative exposure to ICS, which did not control symptoms and placed a burden on the patient's QoL
- Biomarkers: blood eosinophils 200 cells/µL and FeNO 25 ppb

What effects do you expect emerging biological therapies will have on the QoL and long-term management of this patient with T2 asthma?

FeNO, fractional exhaled nitric acid; ICS, inhaled corticosteroids; ppb, parts per billion; QoL, quality of life; T2, type 2.

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