How I do it. Work-up of severe asthma

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ABSTRACT

Case example: A 56-year-old gentleman has difficult to control asthma and a history of four exacerbations in the prior 12 months despite high-dose inhaled corticosteroids (ICS) and additional controller therapies. Is he suitable for more advanced therapeutic options?

Scope of review: We herein review the clinical assessment of a patient with suspected severe asthma, discuss factors contributing to poor asthma control and how biomarkers assist in disease investigation and stratification.

How I do it: The key components of our multidisciplinary approach are to confirm an asthma diagnosis and adherence to treatment, to assess any contributing comorbidities or confounding factors, and to stratify what type of asthma our patient has. The combination of spirometry and repeated measures of key biomarkers of type-2 airway inflammation – the blood eosinophil count and fractional exhaled nitric oxide – identifies whether poor disease control is driven by uncontrolled, ICS-resistant type-2 airway inflammation or ongoing airflow obstruction. A failure to elicit evidence of either suggests an alternative driver for the patient's symptoms including chronic airway infection and non-asthma causes. Each phenotype represents a treatable trait that requires a specific targeted approach. Critically, steroids can cause harm and their use should be guided by objective evidence of inflammation rather than symptoms alone.

Case conclusion: After assessment of treatment adherence and exclusion of relevant comorbidities, the patient was found to have severe asthma with ICS-resistant type-2 airway inflammation. We will consider additional treatment options at our next appointment (Part 2/2 of this How I Do It series). **Word count: 247/250**

ABREVIATIONS

ABPA: allergic bronchopulmonary aspergillosis

ACQ: asthma control questionnaire

CF: cystic fibrosis

CT: computed tomography

EGPA: eosinophilic granulomatosis with polyangiitis

ENT: ear nose throat specialist

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

GERD: gastro-esophageal reflux disease

GI: gastrointestinal

ICS: inhaled corticosteroid

Ig: immunoglobulin

IL: interleukin

MDT: multidisciplinary team

OCS: oral corticosteroids

T2: type-2

Case Example

Dear Colleague,

Please review this 56-year-old gentleman with difficult asthma.

Despite current treatments which include prescription of high-dose combination inhaled corticosteroid (ICS) / long acting beta2-agonist, inhaled long acting muscarinic antagonist and oral leukotriene receptor antagonist, he remains symptomatic and has had four exacerbations requiring oral corticosteroids (OCS) over the last year. He has previously had surgery for nasal polyposis and remains bothered by nasal obstruction and anosmia. He has a dog and a cat. Clinical examination reveals expiratory wheeze. His peak flow today is 350 L/min (predicted 516 L/min).

Many thanks,

Dr GP

Definitions

Most people with asthma have well-controlled symptoms and remain largely exacerbation-free on low to medium-dose inhaled corticosteroids with or without additional treatments. Up to 10% require high intensity treatment to maintain control, or remain uncontrolled despite high intensity treatment[1,2]. These patients with severe asthma account for most of the morbidity, mortality and societal costs attributed to the disease[3].

Many patients initially appear to have severe asthma until a more in-depth evaluation reveals one or more factors that contribute to their ongoing symptom burden and/or exacerbation risk. The term 'difficult-to-treat asthma' has frequently been used to describe this clinical scenario and may often include issues such as suboptimal adherence to ICS

and poor inhaler technique, as well as the incorrect attribution of symptoms to asthma rather than co-morbidities.

The distinction between 'difficult' and 'severe' asthma (Figure 1) remains one of the key functions of a severe asthma clinic and requires a thorough history, a multi-disciplinary team approach including objective assessments of airflow limitation, treatment adherence and suspected co-morbidities, and the routine use of biomarkers of type-2 (T2) airway inflammation.

Workup of severe asthma: our thought process

1. Does this patient have asthma?

It is noteworthy that a third of adults with physician-diagnosed asthma do not have objective evidence of asthma during formal testing[4]. Referrals for asthma of any severity should first aim to confirm the diagnosis by showing variable airflow limitation and excluding other causes or confounding factors.

Airflow limitation is indicated by a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of <0.7 (<0.75-80 in young adults) and usually a FEV_1 <80% predicted. Assessment of reversibility to a rapid onset beta2-agonist or spontaneous within day peak expiratory flow variability from home readings may help demonstrate variable airflow limitation although negative findings are not necessarily helpful[5]. Often in a patient with severe asthma there will be multiple measures of spirometry available in the medical notes and the demonstration of airflow limitation which varies over time and/or following treatment is straightforward. The persistent absence of airflow limitation when symptomatic should alert the clinician to the possibility of an incorrect diagnosis. Assessment of airway

responsiveness via methacholine provocation or exercise challenge is a sensitive measure in these patients with normal or near-normal spirometry[5,6].

2. Is asthma uncontrolled?

The quantification of asthma control should rely on objective parameters. We commonly use severe asthma attack history (defined as acute OCS use ≥ 3 days for asthma) and the 5-item asthma control questionnaire (ACQ-5). The single best predictor for a future asthma attack is the occurrence of an attack in the past year[7]. The ACQ-5 provides an estimate of asthma symptoms during the previous week: a mean score >1.5 suggests poorly controlled asthma, and a clinically significant change between two visits is 0.5[8]. Alternatively, the Asthma Control Test can be used to assess the previous month, with a mean score <20 suggesting poor control and a 3-point difference judged significant[9,10].

3. Is asthma driving the symptoms?

Many patients with correctly diagnosed asthma present with persistent symptoms because of comorbid diseases which may or may not be related to asthma or its treatment[11]. Non-asthma conditions are important to recognize as these cause symptoms which are unlikely to respond to inhaled treatment. Chronic obstructive pulmonary disease, bronchiectasis, breathing pattern disorders, vocal cord dysfunction, obesity, sleep disorders, aspiration (including foreign body aspiration) and steroid-induced complications are commonly involved[12]. Difficulties arise when these conditions co-exist with asthma: this typically results in unsuccessful and often deleterious escalation to maximal therapy. Conversely, identification of comorbidities coinciding with the underlying causal pathway for asthma may increase the likelihood of severe disease and lead to personalized treatment decisions. Chronic rhinosinusitis with nasal polyposis, eczema and urticaria are noteworthy examples where identifying a treatable trait positively impacts disease management[13,14].

Medical history needs to be sufficiently rigorous to account for all these factors. Our 'must ask questions' reflect this (Table 1).

Clinical examination is frequently normal in asthma. Some patients may display features of obstructive airways disease, including a hyperinflated and hyperresonant chest and diffuse polyphonic expiratory wheeze on auscultation. However, examination is more often helpful in identifying signs of an alternative or comorbid diagnosis. Key extrapulmonary systems to examine are the skin (for eczema or other eosinophilic pathologies; the hands for signs of smoking or digital clubbing), the nose (for rhinitis and overt nasal polyposis; an otoscope can be used), and the cardiovascular system (for signs of fluid overload, arrhythmia or heart murmurs).

Finally, in pregnant women with asthma, hormonal fluctuations, overlapping pregnancy-related conditions and incorrect perception of the risk-benefits of continuing their asthma treatments can lead to loss of control[15]. Education is key. Importantly, principles for the investigation and management of suspected severe asthma still apply[15,16].

4. Is the environment causal or modifiable?

Exposure to an adverse environment can be an important correctable factor for uncontrolled asthma. This might be a relevant aspect in the patient described above. Exposure to allergens to which the patient is sensitized or to irritant stimuli such as cigarette smoke are associated with more severe and treatment unresponsive disease and there is evidence that smoking cessation improves asthma control[17]. Unfortunately, there are no clear data supporting allergen avoidance as a means of reducing pharmacological therapy[18].

Occupational asthma should be considered in all patients presenting with adult-onset asthma or a marked change in their asthma control. Indeed, 15% of new onset adult asthma are occupational asthma[19]. Patients may notice that their symptoms are work-related and improve over the weekend or when on holiday. Asthma can be aggravated by work exposures or it can be caused by exposure to a novel respiratory sensitizer at work. In the latter situation there is typically a lag period of exposure before the onset of symptoms, which may initially involve the upper airway. A wide variety of high (*e.g.* flour, latex) and low (*e.g.* isocyanates, acrylates) molecular weight agents can act as respiratory sensitizers and cause occupational asthma. Bakers, healthcare workers and spray painters are at particularly high risk. Removal from the offending workplace can result in improved asthma control, particularly if the occupational cause is identified early[20].

5. Tackling nonadherence: is this severe asthma?

Up to 80% of patients on high-intensity asthma treatment do not have optimal medication intake[2]. The assessment of treatment adherence is therefore a crucial yet often overlooked component of the workup. Distinguishing between intentional and unintentional nonadherence can be helpful. Intentional nonadherence is informed by beliefs, emotions and preferences, whereas unintentional nonadherence is a consequence of forgetfulness, complicated dosing regimens, and/or poor inhaler technique[21]. In both cases, nonadherence implies that the patient is not optimally treated and, accordingly, does not have severe asthma.

Different contexts call for different methods to investigate adherence (Table 2). Arguably the simplest and most accessible method is to carefully document the controller prescription pickup rate and to observe the patient's inhaler technique. The measurement of blood levels of prednisolone or theophylline can also be helpful if these therapies are

prescribed. Poor adherence with ICS should be suspected in a patient with a persistently raised exhaled nitric oxide (FeNO) since this biomarker is generally – but not universally[22] – ICS responsive[23]. A useful approach to the assessment of such a patient is to carry out a FeNO suppression test, during which ICS are delivered in a supervised fashion (*i.e*. using a chipped inhaler) for 7 to 28 days[24,25]. Measuring FeNO before and after the test identifies as many as 50% of patients who significantly suppress their FeNO, a pattern typically associated with a good clinical response to ICS. The demonstration of treatment responsive inflammation may be all that is needed to persuade the patient to adhere to ICS, effectively mitigating intentional and unintentional nonadherence issues. Some patients will derive benefit from alternative approaches including the use of maintenance and reliever ICS/fast-onset beta2-agonist therapy[26,27]. Finally, the use of remotely monitored inhalers (*i.e.* chipped or Bluetooth-enabled devices) can be a useful tool to promote and monitor adherence[28].

The variety of methods and difficulties to address treatment adherence highlights the importance of working with a multidisciplinary team (MDT). We review suspected severe asthma cases before and after clinic with the MDT[29]. From the prescriber's perspective, collaborating with a team of professionals will ensure that each patient has completed the necessary workup to confirm a diagnosis of severe asthma and been assessed for comorbidities and complications of corticosteroid therapy. Professionals who are part of the MDT include respiratory consultants, specialist nurses, a clinical pharmacist, a speech and language therapist, trainees and a coordinator. Selected cases can also benefit from input by Ear Nose and Throat (ENT) or gastrointestinal (GI) specialists. The main outcome for the patient is a holistic, consistent and tailored approach to manage their airways disease

6. What type of severe asthma does the patient have?

A key step is to identify the lower airway inflammatory phenotype. Lower airway pathology is highly heterogeneous in patients with severe asthma[30]. Type-2-high, eosinophilic airway inflammation is mediated by the T2 cytokines IL-4, IL-5 and IL-13[31] and easily identified in clinic by increased levels blood or sputum eosinophils and FeNO[14,22]. The use of biomarkers of T2 airway inflammation (Table 3) as the treatment target has become a key component of corticosteroid stewardship[32]. Indeed, it is important to identify patients with T2-mediated disease who are at increased risk of asthma attacks and respond well to anti-inflammatory treatment[14]. Conversely, presumed T2-low asthma should alert clinicians to look for alternative causes for morbidity (*e.g.* airways infection[33,34]) and to de-escalate corticosteroid therapy[35,36]. As oral corticosteroids suppress T2 inflammation[37], guidelines suggest that one should presume that people on OCS are T2-high; however, it is reassuring to note that biomarker-guided de-escalation of OCS is safe and may also unmask T2 status. With biomarker-guided treatment down-titration, a T2 phenotype becomes evident in up to 95% of patients with severe, uncontrolled asthma[36].

The blood eosinophil count and FeNO (Figure 2) are the most practical and helpful biomarkers to determine the lower airway inflammatory phenotype. While eosinophilic inflammation can be observed with blood eosinophil counts as low as 0.15×10^9/L, T2 inflammation and exacerbations are generally increased with eosinophil counts $\geq0.30\times10^9$/L. Conversely, sputum eosinophilia is unlikely to be present in patients with a blood count $<0.15\times10^9$/L, especially when FeNO is low (<25 ppb)[38]. Raised blood eosinophil counts are also commonly seen in patients with atopic dermatitis so the demonstration of eosinophilia is not a specific marker of T2 lower airway inflammation.

These caveats illustrate the utility of FeNO measurement, which localizes the problem to the airway[22].

Nitric oxide is produced by airway epithelial cells as a result of IL-13-induced induction of nitric oxide synthase in the airway epithelium[39–41] and is therefore a more specific marker of T2 airway inflammation. Values above 25 ppb are indicative of T2 inflammation and are considered significantly increased at levels ≥50ppb. FeNO may be influenced by the level of – and adherence to – ICS, the presence of nasal polyposis (in which levels can be high in the absence of asthma) and smoking (which reduces FeNO levels)[42,43]. Although raised FeNO typically responds to corticosteroids[23], recent evidence shows that FeNO non-suppression in the context of high-intensity therapy identifies corticosteroid-resistant T2 cytokine, chemokine, and alarmin-signaling in the airway compartment[22]. Furthermore, it has been observed in ICS-tapering trials that a doubling of FeNO over 21 days increases the risk of uncontrolled asthma nearly three-fold[44]. Likewise, in the placebo arms of clinical trials for biologics, a raised baseline FeNO (≥50 *vs* <25) was associated with double the severe asthma attack rates for patients with similar blood eosinophilia (≥0.30×10^9/L)[45–48]. In effect, FeNO contributes a different yet complementary information on the T2 inflammatory response; analogous to a magnet (FeNO-related airway chemokines) pulling systemic effector cells (blood eosinophils) to the airway compartment (Figure 2)[22,48]. The predictive value of these two biomarkers is associated with the intensity of the signal and is additive in regards to the identification of T2 inflammation,[14,22,38] the risk of severe asthma attacks[45–48] and the likelihood of a response to specific treatment[47,49].

Confirming atopy with skin-prick testing or measurement of total IgE and allergen-specific IgE may help support a diagnosis of atopic asthma and provide an argument for allergen avoidance and omalizumab prescription in cases in which the allergy is felt to be the

dominant driver of the patient's asthma. The panel of airborne allergens selected for assessment should be refined according to local triggers but in general includes *Aspergillus fumigatus*, house dust mite, seasonal tree/grass/weed pollens and any other significant perennial allergens in the patient's environment (*e.g.* pets).

Finally, sputum cultures are useful to assess for chronic airways infection, which is more often present in neutrophilic, T2-low asthma[33] and can predict response to macrolides when *Haemophilus influenzae* is isolated[34]. Acid-fast bacilli sputum cultures should also be ordered when planning for macrolide therapy[50]. It is noteworthy that increased sputum production and purulence are not necessarily predictive of bacterial infection in severe eosinophilic asthma[51], where bronchorrhea may respond to anti-inflammatory rather than antibiotic therapy.

7. Has imaging been reviewed?

Imaging is not routinely recommended in mild-moderate asthma[52], however, assuming issues relating to poor inhaler adherence/technique have been excluded, it is important to perform at least a chest X-ray and generally a high-resolution chest computed tomography (CT). In the context of high levels of T2 inflammation this can identify features suggestive of an additional eosinophilic lung disease, *e.g.:* allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), or chronic eosinophilic pneumonia. Conversely, in the absence of significant T2 inflammation, evidence of chronic airway infection and/or any non-asthma related pathology including tracheal or parenchymal disease and bronchiectasis can be evident on imaging. In a current or ex-smoker, it will identify any overlapping emphysema.

Chest CT imaging is also an important step if bronchoscopy is considered. Bronchoscopy can identify other comorbidities including vocal cord dysfunction, laryngopharyngeal reflux, fixed airway narrowing and airway infection. It also allows for bronchoalveolar lavage (BAL) and / or endobronchial biopsy studies for evidence of eosinophilia and other inflammatory cells.

Finally, we order a sinus CT in patients reporting symptoms suggestive of chronic rhinosinusitis with nasal polyposis, *i.e.* facial congestion/pain, nasal obstruction, purulent discharge, and/or hyposmia/anosmia lasting 12 weeks or longer[53]. As the effects of high intensity acid suppression therapy are disappointing[54], we do not routinely obtain detailed GI assessments for suspected comorbid gastroesophageal reflux disease; however tailored barium swallow, esophagram and pH probe may uncover GI comorbidities that warrant further treatment in some circumstances

8. Are further tests indicated?

Extra-pulmonary comorbidities are common in severe asthma and investigating an extensive list of differential diagnoses does not necessarily improve outcomes. Accordingly, we do not systematically order all the investigations listed in Table 4 but assess the pretest probability and the likelihood that the test result will change our management of the patient. Certainly, serious consideration should be given to flexible laryngo-bronchoscopy in cases of suspected central airways disease (to eliminate fixed or dynamic proximal airway obstruction); *Strongyloides*/parasite serologies and stool examinations in patients having traveled to at-risk regions; and *Aspergillus*-specific IgG/IgE plus anti-neutrophil cytoplasmic antibodies in cases of significant blood eosinophilia. We order detailed hypereosinophilic syndrome work-up (FIP1L1/PDGFRA: responds to imatinib) for cases with extreme hypereosinophilia (>5.0 $\times 10^9$/L), or hypereosinophilia (1.5 $\times 10^9$/L) with other suspect features[55].

Perhaps the only exception to the test-then-treat rule for comorbidities is the occasional case in which eosinophilic granulomatosis with polyangiitis (EGPA) is seriously entertained. In a high-risk clinical setting, we consider starting systemic corticosteroids prior to receiving antibody results – which are positive in less than half of patients with EGPA – and even prior to performing tissue biopsy, as untreated disease carries the risk of serious morbidity (*e.g.* stroke with neurologic sequelae, cardiomyopathy)[56].

Corticosteroids have metabolic effects that should be investigated on a case-by-case basis. Most patients experience one or more steroid-induced complication(s) such as obesity, psychiatric disorders, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, adrenal insufficiency, osteoporosis, cataracts, glaucoma, dyspeptic disorders, and sepsis/infection. These adverse effects are dose-related across

the range of doses of prednisone used in asthma but can develop from as little as 4 short courses of high dose steroids / year[57] and they accumulate with time[58,59]. Patients with severe OCS-dependent asthma should be assessed formally as they may suffer from significant morbidity when complications are not recognized and managed. We ensure that glycosylated hemoglobin, blood pressure monitoring, bone density measurement and ophthalmologist examination has been recently performed in these patients.

How we do it.

We work with and as a team. We have devised a standard pathway for patients that are referred to our 'special airways clinic' (Figure 3). As the name implies, we avoid labels and focus on the identification of relevant mechanisms, or treatable traits. Our MDT meeting allows for a many-sided approach which expedites investigation and management plans. The overbearing principle is that we identify and treat mechanisms rather than potentially unrelated symptoms. We align treatment intensity according to disease severity, rather than the other way around.

Case conclusion

Prior to our first encounter, the MDT reviewed the referral letter and asked for our pharmacist to perform an adherence check, which confirmed a 100% treatment pickup rate. On the day of the appointment, our nurse reviewed his inhaler technique (good), obtained an ACQ score (3.2; over 1.5 is uncontrolled) and measured FeNO (high at 78 ppb). Spirometry confirmed reversible airflow limitation with moderate obstruction (post bronchodilator FEV_1 72% predicted; FEV_1/FVC 0.62). Medical history and physical examination suggested adult-onset severe asthma with comorbid chronic rhinosinusitis and nasal polyposis. This gentleman recalls improvement in his wheezing, nasal obstruction and anosmia within 24 hours to prednisone when he last had a course for an

asthma attack implying that type-2 airway inflammation is likely to be the dominant mechanism driving both his lower and upper airway disease. Further investigations showed raised blood eosinophils (0.76×10^9 cells/L) and total IgE (364 kU/L), with a single weakly positive specific-IgE (*Aspergillus fumigatus*). Current and previous Chest X-rays, as well as a chest CT performed two years ago were reviewed and judged unremarkable.

After the clinic, the MDT reconvened. We discussed and agreed that this patient has T2-high, severe, uncontrolled asthma despite good adherence to ICS. Although sensitized to *Aspergillus*, his relatively low total IgE and imaging are against ABPA contributing to his disease. He likely has recurrence of his nasal polyposis, and we have ordered a sinus CT, optimized his nasal therapy and prescribed a standby rescue pack of prednisone 40 mg p.o. x5 days.

At our next appointment we will review his sinus CT and any other outstanding investigations and discuss further treatment options.

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Figure legends

FIGURE 1

Symptoms and treatment intensity define difficult asthma and severe asthma, whereas biomarkers of type-2 airway inflammation suggest the disease phenotype. There is an acknowledged indeterminate zone between biomarker cut points for type-2 high and type-2 low. A severe asthma attack is defined by a burst of systemic corticosteroids for > 3 days. ACQ = asthma-control questionnaire, ACT = asthma control test, Blood Eos = peripheral blood eosinophil count (x10^9 cells/L), FeNO = fractional exhaled nitric oxide (ppb), Sputum Eos = sputum eosinophils (%).

FIGURE 2

Translating type-2 (T2) biomarkers in severe asthma: a two-compartment, two-hit theory. Fractional exhaled nitric oxide (FeNO) and the peripheral blood eosinophil count provide mechanistic information from distinct immune compartments: FeNO reflects airway type-2 activity and the chemotactic pull to the airway compartment, whilst blood eosinophils reflect the systemic pool of available effector cells and circulating interleukin (IL)-5[22]. These biomarkers have additive value in predicting severe asthma attacks in the control arm of clinical trials[45–48]. Under this two-compartment-two-hit model, a trigger (*e.g.* a virus or allergen) leads to a multiplicative event – the asthma attack[60,61]. ICS, inhaled corticosteroid, TARC, thymus activation regulated cytokine; TSLP, thymic stromal lymphopoietin.

FIGURE 3

A suggested algorithm for assessing and managing patients with severe asthma. * = Adherence (*e.g.* ≥ 75% prescription pick-up rate; see Table 2) is ideally assessed in every new patient, but must certainly be confirmed prior to biological prescription; # = biomarker

high, *i.e.* blood eosinophil cell counts ≥0.15×10^9 cells/L and/or fractional exhaled nitric oxide ≥25 ppb; † = usually a combination of long-acting bronchodilator/low-dose inhaled corticosteroid (ICS) plus a long-acting muscarinic; ACQ = asthma-control questionnaire; IgE = immunoglobulin E; MART = maintenance and reliever therapy. ACQ = asthma-control questionnaire; IgE = immunoglobulin E.

TABLE 1: 'Must be asked' elements on clinical history in suspected severe asthma

Etiology and contributing factors
Occupation and exposure history
Household pets, dusty or moldy environments
Known allergies, associated symptoms ± confirmatory testing
Aspirin/COX-1 inhibitor sensitivity
Smoking and vaping history
Illicit inhaled drug use: smoked, snorted or vaporized
Pregnancy
Psychosocial stressors
Asthma & asthma attack history
Age of asthma onset, method of diagnosis
Previous intensive care / intubation for asthma
Number of asthma attacks requiring corticosteroids and/or hospital admissions
Number of lower respiratory tract infections requiring antibiotics
Usual triggers and symptoms of attacks
Current asthma control (*e.g.* ACQ, ACT, or GINA control checklist)
Response to systemic corticosteroids: significant and prompt response suggests eosinophilic airway pathology
Current and previous asthma therapies
Current treatment regimen, including over-the-counter medications
Controller and reliever therapies felt to be helpful – pattern of use and response
Controller and reliever therapies felt to be unhelpful – previous treatment failures
Barriers to treatment adherence
Vaccination history

Comorbidity assessment
Cardiovascular and metabolic comorbidities; ischemic heart disease, diabetes, (…)
Common type-2-high comorbidities: especially nose, sinus and skin disease
Common type-2-unrelated comorbidities: anxiety/depression, recurrent chest infections, gastroesophageal reflux disease, (…)
Common respiratory red flags and/or symptoms of ‘asthma plus’ conditions: ABPA, CEP, EGPA, (…)

ABPA = allergic bronchopulmonary aspergillosis, ACQ = asthma control questionnaire, ACT = asthma control test,CEP = chronic eosinophilic pneumonia, EGPA = eosinophilic granulomatosis with polyangiitis, GINA = global initiative for asthma

TABLE 2. Methods used to assess treatment adherence in severe asthma

Method	Association with outcomes	Logistics	Comments
Prescription records	Solid evidence that patients with low consumption of ICS do less well	Simple in most health care systems	Does not assess treatment use directly. Accurate information not always available.
Blood drug levels	Has not been associated with clinical outcomes	Widely available	Only applicable for theophylline and prednisolone. Undetectable prednisolone and / or normal serum cortisol generally accepted as a reliable marker of non-adherence to maintenance prednisolone.
FeNO suppression test[24,25]	Significant suppression of FeNO after 7 to 28-day monitored ICS therapy is associated with longer-term response to supervised treatment	Difficult to carry out in most healthcare systems	Some patients better understand the positive impact of ICS treatment by seeing a measurable decrease in their airway inflammation matching their clinical improvement.
Remote monitoring of chipped inhaler devices[28]	Allows real-time monitoring of adherence to asthma treatments May improve adherence and decrease exacerbations in research settings	'Chipped inhaler' technology varies with inhaler type	Increasingly carried out in severe asthma clinics. Technology and wireless communication capacities rapidly evolving.

FeNO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid.

TABLE 3: Biomarkers of Type-2 Airway Inflammation

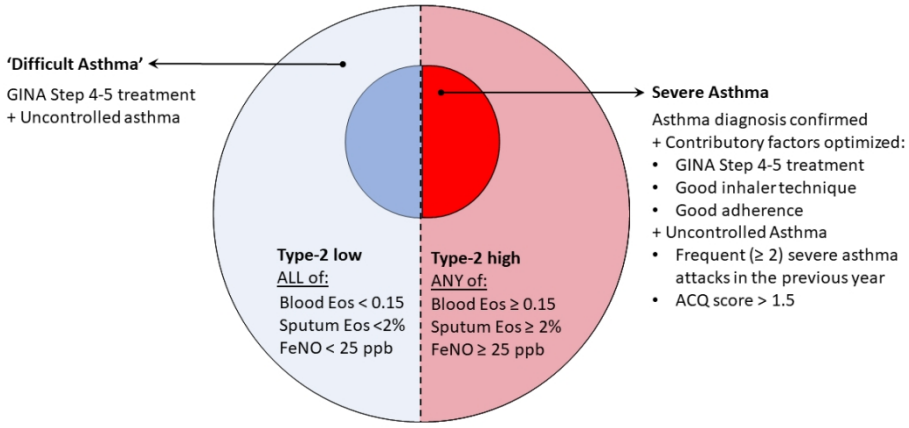
Biomarker	Cut-offs	Association with treatment response	Comments
IgE	Variable	Anti-IgE	IgE levels do not consistently predict clinical outcomes nor treatment responsiveness
Blood eosinophil count	≥ 0.15×10^9 per L	Corticosteroids Anti-IL-5/5R Anti-IL4Rα Anti-IgE Anti-TSLP	Generally available, cheap, directly relates to asthma control and risk of asthma attacks
Sputum eosinophils	≥ 2%	Corticosteroids Anti-IL-5 Anti-IL4Rα	Not routinely available, tissue specific, time-consuming
FeNO	≥25 ppb	ICS Anti-IL-4Rα Anti-TSLP	Quick, cheap, non-invasive, associated with increased risk of asthma attacks; increases probability of ICS-responsiveness

FeNO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid, Ig = immunoglobulin, IL = interleukin, R = receptor. TSLP = thymic stromal lymphopoietin. Modified from reference 14.

TABLE 4: Suspected contributing factors to severe asthma and their investigations

Suspected problem	Possible investigation
Bronchiectasis, emphysema, large airway pathology	High-resolution chest CT (inspiratory and expiratory images) ± bronchoscopy
Chronic airways infection	Sputum cultures (×2), including for acid-fast bacilli ± bronchoscopy
Chronic rhinosinusitis with nasal polyposis	Sinus CT ± nasoendoscopy / ENT referral
Corticosteroid-induced side effects	Specific to target organ, but may include: glycosylated hemoglobin, blood pressure monitoring, 8 a.m. cortisol, bone density measurement, ophthalmologist referral
Cystic fibrosis	Sweat chloride ± genetic testing
Dysfunctional breathing pattern*	Respiratory physiotherapy assessment
Dyspepsia, GERD#	GI referral for esophageal manometry, pH monitoring and/or endoscopy
Helminth infection	Specific to travel history, but may include: stool microscopy exam for parasitic ova and larvae, *Stronglyoides* and/or *Schistosomiasis* serology
Hypereosinophilic syndromes	Hematology referral for cytogenetics (FIP1L1/PDGFRA) and/or further testing[55]
Immunodeficiency	IgG, IgM, IgA ± immunology referral
Inducible laryngeal obstruction	ENT / speech and language therapy with dynamic laryngoscopy
Obstructive sleep apnea or other sleep disordered breathing	Sleep study
Unexplained breathlessness	Echocardiogram and full pulmonary function tests ± CPET
Vasculitis	Anti-neutrophil cytoplasmic antibodies ± affected tissue (*e.g.* skin, nose, nerve or lung) biopsy

* In cases where dysfunctional breathing overlaps with persistent type-2 inflammation, the latter entity can be treated in parallel; #Gastro-esophageal reflux disease (GERD) investigation and treatment is unlikely to result in improved asthma control[54]. CF = cystic fibrosis, CPET = cardiopulmonary exercise testing, CT = computed tomography, ENT = ear-nose-throat surgery, Ig = immunoglobulin, SALT = speech and language therapy.



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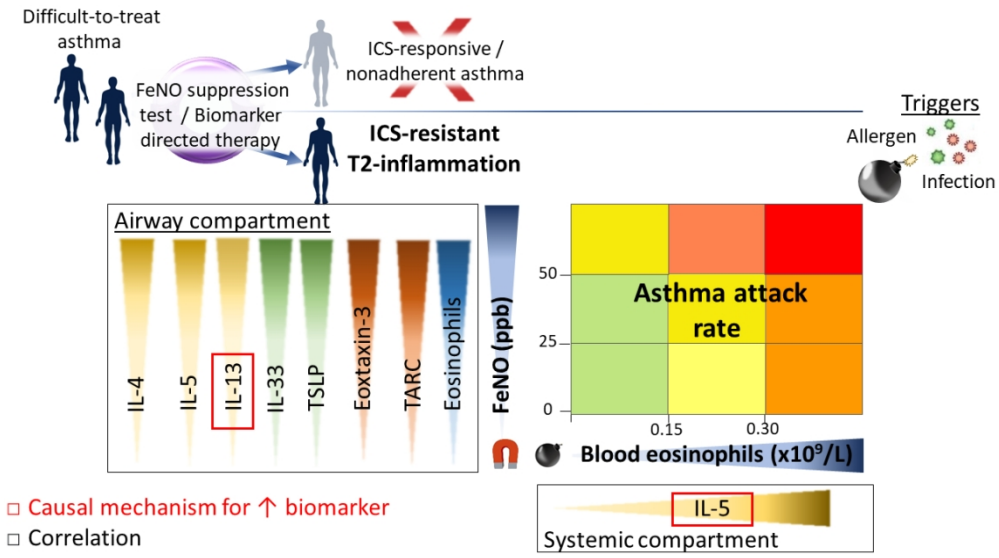

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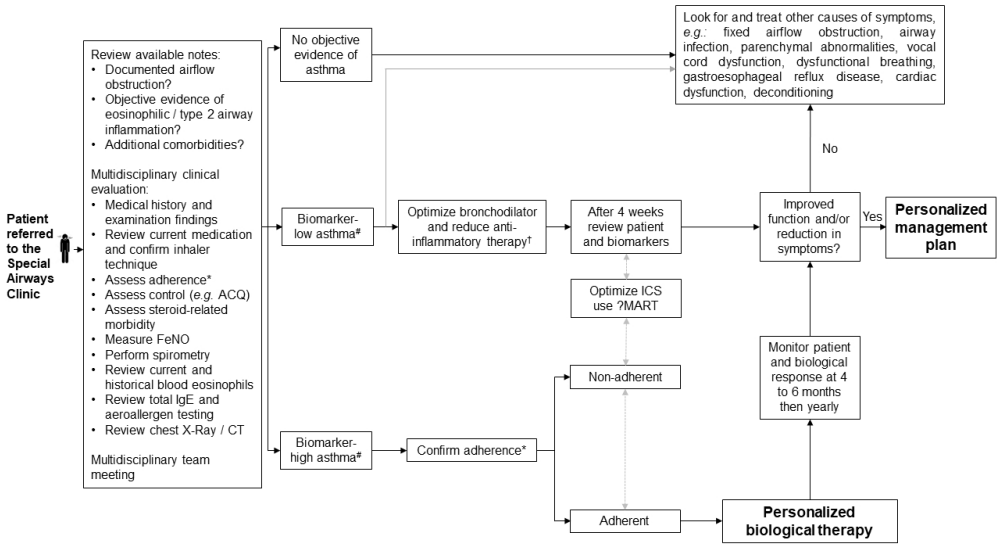

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TITLE: How I do it. Work-up of severe asthma

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ABSTRACT

Case example: A 56-year-old gentleman has difficult to control asthma and a history of four exacerbations in the prior 12 months despite high-dose inhaled corticosteroids (ICS) and additional controller therapies. Is he suitable for more advanced therapeutic options?

Scope of review: We herein review the clinical assessment of a patient with suspected severe asthma, discuss factors contributing to poor asthma control and how biomarkers assist in disease investigation and stratification.

How I do it: The key components of our multidisciplinary approach are to confirm an asthma diagnosis and adherence to treatment, to assess any contributing comorbidities or confounding factors, and to stratify what type of asthma our patient has. The combination of spirometry and repeated measures of key biomarkers of type-2 airway inflammation – the blood eosinophil count and fractional exhaled nitric oxide – identifies whether poor disease control is driven by uncontrolled, ICS-resistant type-2 airway inflammation or ongoing airflow obstruction. A failure to elicit evidence of either suggests an alternative driver for the patient's symptoms including chronic airway infection and non-asthma causes. Each phenotype represents a treatable trait that requires a specific targeted approach. Critically, steroids can cause harm and their use should be guided by objective evidence of inflammation rather than symptoms alone.

Case conclusion: After assessment of treatment adherence and exclusion of relevant comorbidities, the patient was found to have severe asthma with ICS-resistant type-2 airway inflammation. We will consider additional treatment options at our next appointment (Part 2/2 of this How I Do It series). **Word count: 247/250**

ABREVIATIONS

ABPA: allergic bronchopulmonary aspergillosis

ACQ: asthma control questionnaire

CF: cystic fibrosis

CT: computed tomography

EGPA: eosinophilic granulomatosis with polyangiitis

ENT: ear nose throat specialist

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in one second

FVC: forced vital capacity

GERD: gastro-esophageal reflux disease

GI: gastrointestinal

ICS: inhaled corticosteroid

Ig: immunoglobulin

IL: interleukin

MDT: multidisciplinary team

OCS: oral corticosteroids

T2: type-2

Case Example

Dear Colleague,

Please review this 56-year-old gentleman with difficult asthma.

Despite current treatments which include prescription of high-dose combination inhaled corticosteroid (ICS) / long acting beta2-agonist, inhaled long acting muscarinic antagonist and oral leukotriene receptor antagonist, he remains symptomatic and has had four exacerbations requiring oral corticosteroids (OCS) over the last year. He has previously had surgery for nasal polyposis and remains bothered by nasal obstruction and anosmia. He has a dog and a cat. Clinical examination reveals expiratory wheeze. His peak flow today is 350 L/min (predicted 516 L/min).

Many thanks,

Dr GP

Definitions

Most people with asthma have well-controlled symptoms and remain largely exacerbation-free on low to medium-dose inhaled corticosteroids with or without additional treatments. Up to 10% require high intensity treatment to maintain control, or remain uncontrolled despite high intensity treatment[1,2]. These patients with severe asthma account for most of the morbidity, mortality and societal costs attributed to the disease[3].

Many patients initially appear to have severe asthma until a more in-depth evaluation reveals one or more factors that contribute to their ongoing symptom burden and/or exacerbation risk. The term 'difficult-to-treat asthma' has frequently been used to describe this clinical scenario and may often include issues such as suboptimal adherence to ICS

and poor inhaler technique, as well as the incorrect attribution of symptoms to asthma rather than co-morbidities.

The distinction between 'difficult' and 'severe' asthma (Figure 1) remains one of the key functions of a severe asthma clinic and requires a thorough history, a multi-disciplinary team approach including objective assessments of airflow limitation, treatment adherence and suspected co-morbidities, and the routine use of biomarkers of type-2 (T2) airway inflammation.

Workup of severe asthma: our thought process

1. Does this patient have asthma?

It is noteworthy that a third of adults with physician-diagnosed asthma do not have objective evidence of asthma during formal testing[4]. Referrals for asthma of any severity should first aim to confirm the diagnosis by showing variable airflow limitation and excluding other causes or confounding factors.

Airflow limitation is indicated by a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) of <0.7 (<0.75-80 in young adults) and usually a FEV_1 <80% predicted. Assessment of reversibility to a rapid onset beta2-agonist or spontaneous within day peak expiratory flow variability from home readings may help demonstrate variable airflow limitation although negative findings are not necessarily helpful[5]. Often in a patient with severe asthma there will be multiple measures of spirometry available in the medical notes and the demonstration of airflow limitation which varies over time and/or following treatment is straightforward. The persistent absence of airflow limitation when symptomatic should alert the clinician to the possibility of an incorrect diagnosis. Assessment of airway

responsiveness via methacholine provocation or exercise challenge is a sensitive measure in these patients with normal or near-normal spirometry[5,6].

2. Is asthma uncontrolled?

The quantification of asthma control should rely on objective parameters. We commonly use severe asthma attack history (defined as acute OCS use ≥ 3 days for asthma) and the 5-item asthma control questionnaire (ACQ-5). The single best predictor for a future asthma attack is the occurrence of an attack in the past year[7]. The ACQ-5 provides an estimate of asthma symptoms during the previous week: a mean score >1.5 suggests poorly controlled asthma, and a clinically significant change between two visits is 0.5[8]. Alternatively, the Asthma Control Test can be used to assess the previous month, with a mean score <20 suggesting poor control and a 3-point difference judged significant[9,10].

3. Is asthma driving the symptoms?

Many patients with correctly diagnosed asthma present with persistent symptoms because of comorbid diseases which may or may not be related to asthma or its treatment[11]. Non-asthma conditions are important to recognize as these cause symptoms which are unlikely to respond to inhaled treatment. Chronic obstructive pulmonary disease, bronchiectasis, breathing pattern disorders, vocal cord dysfunction, obesity, sleep disorders[12], aspiration (including foreign body aspiration) and steroid-induced complications are commonly involved[12]. Difficulties arise when these conditions co-exist with asthma: this typically results in unsuccessful and often deleterious escalation to maximal therapy. Conversely, identification of comorbidities coinciding with the underlying causal pathway for asthma may increase the likelihood of severe disease and lead to personalized treatment decisions. Chronic rhinosinusitis with nasal polyposis, eczema and urticaria are noteworthy examples where identifying a treatable trait positively impacts disease management[13,14].

Medical history needs to be sufficiently rigorous to account for all these factors. Our 'must ask questions' reflect this (Table 1).

Clinical examination is frequently normal in asthma. Some patients may display features of obstructive airways disease, including a hyperinflated and hyperresonant chest and diffuse polyphonic expiratory wheeze on auscultation. However, examination is more often helpful in identifying signs of an alternative or comorbid diagnosis. Key extrapulmonary systems to examine are the skin (for eczema or other eosinophilic pathologies; the hands for signs of smoking or digital clubbing), the nose (for rhinitis and overt nasal polyposis; an otoscope can be used), and the cardiovascular system (for signs of fluid overload, arrhythmia or heart murmurs).

Finally, in pregnant women with asthma, hormonal fluctuations, overlapping pregnancy-related conditions and incorrect perception of the risk-benefits of continuing their asthma treatments can lead to loss of control[15]. Education is key. Importantly, principles for the investigation and management of suspected severe asthma still apply[15,16].

4. Is the environment causal or modifiable?

Exposure to an adverse environment can be an important correctable factor for uncontrolled asthma. This might be a relevant aspect in the patient described above. Exposure to allergens to which the patient is sensitized or to irritant stimuli such as cigarette smoke are associated with more severe and treatment unresponsive disease and there is evidence that smoking cessation improves asthma control[17]. Unfortunately, there are no clear data supporting allergen avoidance as a means of reducing pharmacological therapy[18].

Occupational asthma should be considered in all patients presenting with adult-onset asthma or a marked change in their asthma control. Indeed, 15% of new onset adult asthma are occupational asthma[19]. Patients may notice that their symptoms are work-related and improve over the weekend or when on holiday. Asthma can be aggravated by work exposures or it can be caused by exposure to a novel respiratory sensitizer at work. In the latter situation there is typically a lag period of exposure before the onset of symptoms, which may initially involve the upper airway. A wide variety of high (*e.g.* flour, latex) and low (*e.g.* isocyanates, acrylates) molecular weight agents can act as respiratory sensitizers and cause occupational asthma. Bakers, healthcare workers and spray painters are at particularly high risk. Removal from the offending workplace can result in improved asthma control, particularly if the occupational cause is identified early[20].

5. Tackling nonadherence: is this severe asthma?

Up to 80% of patients on high-intensity asthma treatment do not have optimal medication intake[2]. The assessment of treatment adherence is therefore a crucial yet often overlooked component of the workup. Distinguishing between intentional and unintentional nonadherence can be helpful. Intentional nonadherence is informed by beliefs, emotions and preferences, whereas unintentional nonadherence is a consequence of forgetfulness, complicated dosing regimens, and/or poor inhaler technique[21]. In both cases, nonadherence implies that the patient is not optimally treated and, accordingly, does not have severe asthma.

Different contexts call for different methods to investigate adherence (Table 2). Arguably the simplest and most accessible method is to carefully document the controller prescription pickup rate and to observe the patient's inhaler technique. The measurement of blood levels of prednisolone or theophylline can also be helpful if these therapies are

prescribed. Poor adherence with ICS should be suspected in a patient with a persistently raised exhaled nitric oxide (FeNO) since this biomarker is generally – but not universally[22] – ICS responsive[23]. A useful approach to the assessment of such a patient is to carry out a FeNO suppression test, during which ICS are delivered in a supervised fashion (*i.e*. using a chipped inhaler) for 7 to 28 days[24,25]. Measuring FeNO before and after the test identifies as many as 50% of patients who significantly suppress their FeNO, a pattern typically associated with a good clinical response to ICS. The demonstration of treatment responsive inflammation may be all that is needed to persuade the patient to adhere to ICS, effectively mitigating intentional and unintentional nonadherence issues. Some patients will derive benefit from alternative approaches including the use of maintenance and reliever ICS/fast-onset beta2-agonist therapy[26,27]. Finally, the use of ~~smart~~ remotely monitored inhalers (*i.e.* chipped or Bluetooth-enabled devices) can be a useful tool to promote and monitor ~~continued~~ adherence[28].

The variety of methods and difficulties to address treatment adherence highlights the importance of working with a multidisciplinary team (MDT). We review suspected severe asthma cases before and after clinic with the MDT[29]. From the prescriber's perspective, collaborating with a team of professionals will ensure that each patient has completed the necessary workup to confirm a diagnosis of severe asthma and been assessed for comorbidities and complications of corticosteroid therapy. Professionals who are part of the MDT include respiratory consultants, specialist nurses, a clinical pharmacist, a speech and language therapist, trainees and a coordinator. Selected cases can also benefit from input by Ear Nose and Throat (ENT) or gastrointestinal (GI) specialists. The main outcome for the patient is a holistic, consistent and tailored approach to manage their airways disease

6. What type of severe asthma does the patient have?

A key step is to identify the lower airway inflammatory phenotype. Lower airway pathology is highly heterogeneous in patients with severe asthma[30]. Type-2-high, eosinophilic airway inflammation is mediated by the T2 cytokines IL-45, IL-513 and IL-134[31] and easily identified in clinic by increased levels blood or sputum eosinophils and FeNO[14,22]. The use of biomarkers of T2 airway inflammation (Table 3) as the treatment target has become a key component of corticosteroid stewardship[32]. Indeed, it is important to identify patients with T2-mediated disease who are at increased risk of asthma attacks and respond well to anti-inflammatory treatment[14]. Conversely, presumed T2-low asthma should alert clinicians to look for alternative causes for morbidity (*e.g.* airways infection[33,34]) and to de-escalate corticosteroid therapy[35,36]. As oral corticosteroids suppress T2 inflammation[37], guidelines suggest that one should presume that people on OCS are ~~Type~~ T2 ~~-~~high; however, it is reassuring to note that biomarker-guided de-escalation of OCS is safe and may also unmask T2 status. With biomarker-guided treatment down-titration, a T2 phenotype becomes evident in up to 95% of patients with severe, uncontrolled asthma[36].

The blood eosinophil count and FeNO (Figure 2) are the most practical and helpful biomarkers to determine the lower airway inflammatory phenotype. While eosinophilic inflammation can be observed with blood eosinophil counts as low as 0.15×10^9/L, T2 inflammation and exacerbations are generally increased with eosinophil counts ≥0.30×10^9/L. ~~The blood eosinophil count is usually ≥0.3×10^9/L in patients with active eosinophilic airway inflammation.~~ Conversely, sputum eosinophilia is unlikely to be present in patients with a blood count <0.15×10^9/L, especially when FeNO is low (<25 ppb)[38]. Raised blood eosinophil counts are also commonly seen in patients with atopic dermatitis so the demonstration of eosinophilia is not a specific marker of T2 lower airway

inflammation.~~: this~~ These caveats illustrate~~s~~ the utility of FeNO measurement, which localizes the problem to the airway[22].

Nitric oxide is produced by airway epithelial cells as a result of IL-13-induced induction of nitric oxide synthase in the airway epithelium[39–41] and is therefore a more specific marker of ~~type 2~~T2 airway inflammation.~~-~~ Values above 25 ppb are indicative of T2 inflammation and are considered significantly increased at levels ≥50ppb. FeNO may be influenced by the level of – and adherence to – ICS, the presence of nasal polyposis (in which levels can be high in the absence of asthma) and smoking (which reduces FeNO levels)~~Values are considered increased at levels ≥50ppb and will be influenced by the level of – and adherence to – ICS, the presence of nasal polyposis (in which levels can be high in the absence of asthma) and smoking (which reduces FeNO levels)[42,43].~~ Although raised FeNO ~~is strongly associated with a positive response~~typically responds to corticosteroids[23], recent evidence shows that FeNO non-suppression in the context of high-intensity therapy identifies corticosteroid-resistant T2 cytokine, chemokine, and alarmin-signaling in the airway compartment[22]. Furthermore, it has been observed in ICS-tapering trials that a doubling of FeNO over 21 days increases the risk of uncontrolled asthma nearly three-fold[44]. Likewise, in the placebo arms of clinical trials for biologics, a raised baseline FeNO (≥50 *vs* <25) was associated with double the severe asthma attack rates for patients with similar blood eosinophilia (≥0.30×10^9/L)[45–48]. In effect, FeNO contributes a different yet complementary information on the T2 inflammatory response; analogous to a magnet (FeNO-related airway chemokines) pulling systemic effector cells (blood eosinophils) to the airway compartment (Figure 2)[22,48]. ~~Values are considered increased at levels ≥50ppb and will be influenced by the level of – and adherence to – ICS, the presence of nasal polyposis (in which levels can be high in the absence of asthma) and smoking (which reduces FeNO levels)[44,45].~~ The predictive value of these two biomarkers is associated with

the intensity of the signal and is additive in regards to the identification of ~~airway eosinophilic~~T2 inflammation,[14,22,38] the risk of severe asthma attacks[45–48] and the likelihood of a response to specific treatment[47,49~~42,48~~].

Confirming atopy with skin-prick testing or measurement of total IgE and allergen-specific IgE may help support a diagnosis of atopic asthma and provide an argument for allergen avoidance and omalizumab prescription in cases in which the allergy is felt to be the dominant driver of the patient's asthma. The panel of airborne allergens selected for assessment should be refined according to local triggers but in general includes *Aspergillus fumigatus*, house dust mite, seasonal tree/grass/weed pollens and any other significant perennial allergens in the patient's environment (*e.g.* pets).

Finally, sputum cultures are useful to assess for chronic airways infection, which is more often present in neutrophilic, T2-low asthma[33] and can predict response to macrolides when *Haemophilus influenzae* is isolated[34]. Acid-fast bacilli sputum cultures should also be ordered when planning for macrolide therapy[50]. It is noteworthy that increased sputum production and purulence are not necessarily predictive of bacterial infection in severe eosinophilic asthma[51], where bronchorrhea may respond to anti-inflammatory rather than antibiotic therapy.

7. Has imaging been reviewed?

Imaging is not routinely recommended in mild-moderate asthma[52], however, assuming issues relating to poor inhaler adherence/technique have been excluded, it is important to perform at least a chest X-ray and generally a high-resolution chest computed tomography (CT). In the context of high levels of T2 inflammation this can identify features suggestive of an additional eosinophilic lung disease, *e.g.:* allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA), or chronic eosinophilic pneumonia. Conversely, in the absence of significant T2 inflammation, evidence of chronic airway infection and/or any non-asthma related pathology including tracheal or parenchymal disease and bronchiectasis can be evident on imaging. In a current or ex-smoker, it will identify any overlapping emphysema.

Chest CT imaging is also an important step if bronchoscopy is considered. Bronchoscopy can identify other comorbidities including vocal cord dysfunction, laryngopharyngeal reflux, fixed airway narrowing and airway infection. It also allows for bronchoalveolar lavage (BAL) and / or endobronchial biopsy studies for evidence of eosinophilia and other inflammatory cells.

Finally, we order a sinus CT in patients reporting symptoms suggestive of chronic rhinosinusitis with nasal polyposis, *i.e.* facial congestion/pain, nasal obstruction, purulent discharge, and/or hyposmia/anosmia lasting 12 weeks or longer[53]. As the effects of high intensity acid suppression therapy are disappointing[54], we do not routinely obtain detailed GI assessments for suspected comorbid gastroesophageal reflux disease; however tailored barium swallow, esophagram and pH probe may uncover GI comorbidities that warrant further treatment in some circumstances

8. Are further tests indicated?

Extra-pulmonary comorbidities are common in severe asthma and investigating an extensive list of differential diagnoses does not necessarily improve outcomes. Accordingly, we do not systematically order all the investigations listed in Table 4 but assess the pretest probability and the likelihood that the test result will change our management of the patient. Certainly, serious consideration should be given to flexible laryngo-bronchoscopy in cases of suspected central airways disease (to eliminate fixed or dynamic proximal airway obstruction); *Strongyloides*/parasite serologies and stool examinations in patients having traveled to at-risk regions; and *Aspergillus*-specific IgG/IgE plus anti-neutrophil cytoplasmic antibodies in cases of significant blood eosinophilia. We order detailed hypereosinophilic syndrome work-up (FIP1L1/PDGFRA: responds to imatinib) for cases with extreme hypereosinophilia (>5.0 $\times 10^9$/L), or hypereosinophilia (1.5 $\times 10^9$/L) with other suspect features[55].

Perhaps the only exception to the test-then-treat rule for comorbidities is the occasional case in which eosinophilic granulomatosis with polyangiitis (EGPA) is seriously entertained. In a high-risk clinical setting, we consider starting systemic corticosteroids prior to receiving antibody results – which are positive in less than half of patients with EGPA – and even prior to performing tissue biopsy, as untreated disease carries the risk of serious morbidity (*e.g.* stroke with neurologic sequelae, cardiomyopathy)[56].

Corticosteroids have metabolic effects that should be investigated on a case-by-case basis. Most patients experience one or more steroid-induced complication(s) such as obesity, psychiatric disorders, hypertension, diabetes, hypercholesterolemia, cardiovascular disease, adrenal insufficiency, osteoporosis, cataracts, glaucoma, dyspeptic disorders, and sepsis/infection. These adverse effects are dose-related across

the range of doses of prednisone used in asthma but can develop from as little as 4 short courses of high dose steroids / year[57] and they accumulate with time[58,59]. Patients with severe OCS-dependent asthma should be assessed formally as they may suffer from significant morbidity when complications are not recognized and managed. We ensure that glycosylated hemoglobin, blood pressure monitoring, bone density measurement and ophthalmologist examination has been recently performed in these patients.

How we do it.

We work with and as a team. We have devised a standard pathway for patients that are referred to our 'special airways clinic' (Figure 3). As the name implies, we avoid labels and focus on the identification of relevant mechanisms, or treatable traits. Our MDT meeting allows for a many-sided approach which expedites investigation and management plans. The overbearing principle is that we identify and treat mechanisms rather than potentially unrelated symptoms. We align treatment intensity according to disease severity, rather than the other way around.

Case conclusion

Prior to our first encounter, the MDT reviewed the referral letter and asked for our pharmacist to perform an adherence check, which confirmed a 100% treatment pickup rate. On the day of the appointment, our nurse reviewed his inhaler technique (good), obtained an ACQ score (3.2; over 1.5 is uncontrolled) and measured FeNO (high at 78 ppb). Spirometry confirmed reversible airflow limitation with moderate obstruction (post bronchodilator FEV_1 72% predicted; FEV_1/FVC 0.62). Medical history and physical examination suggested adult-onset severe asthma with comorbid chronic rhinosinusitis and nasal polyposis. This gentleman recalls improvement in his wheezing, nasal obstruction and anosmia within 24 hours to prednisone when he last had a course for an

asthma attack implying that type-2 airway inflammation is likely to be the dominant mechanism driving both his lower and upper airway disease. Further investigations showed raised blood eosinophils (0.76×10^9 cells/L) and total IgE (364 kU/L), with a single weakly positive specific-IgE (*Aspergillus fumigatus*). Current and previous Chest X-rays, as well as a chest CT performed two years ago were reviewed and judged unremarkable.

After the clinic, the MDT reconvened. We discussed and agreed that this patient has T2-high, severe, uncontrolled asthma despite good adherence to ICS. Although sensitized to *Aspergillus*, his relatively low total IgE and imaging are against ABPA contributing to his disease. He likely has recurrence of his nasal polyposis, and we have ordered a sinus CT, optimized his nasal therapy and prescribed a standby rescue pack of prednisone 40 mg p.o. x5 days.

At our next appointment we will review his sinus CT and any other outstanding investigations and discuss further treatment options.

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Figure legends

~~Figure 1~~**FIGURE 1**

Symptoms and treatment intensity define difficult asthma and severe asthma, whereas biomarkers of type-2 airway inflammation suggest the disease phenotype. There is an acknowledged indeterminate zone between biomarker cut points for type-2 high and type-2 low. A severe asthma attack is defined by a burst of systemic corticosteroids for > 3 days. ACQ = asthma-control questionnaire, ACT = asthma control test, Blood Eos = peripheral blood eosinophil count (x10^9 cells/L), FeNO = fractional exhaled nitric oxide (ppb), Sputum Eos = sputum eosinophils (%).

~~Figure 2~~**FIGURE 2**

~~**Simple tests of**~~Translating type-2 (T2) biomarkers in severe asthma: a two-compartment, two-hit theory.~~**airway inflammation.** Interleukin (IL)-4, IL-5 and IL-13 are pivotal cytokines in the type-2 inflammatory response.~~ Fractional exhaled nitric oxide (FeNO) and the peripheral blood eosinophil count provide mechanistic information from distinct immune compartments: FeNO reflects airway type-2 activity and the chemotactic pull to the airway compartment, whilst blood eosinophils reflect the systemic pool of available effector cells and circulating interleukin (IL)-5[22]. These biomarkers have additive value in predicting severe asthma attacks in the control arm of clinical trials[45–48]. Under this two-compartment-two-hit model, a trigger (*e.g.* a virus or allergen) leads to a multiplicative event – the asthma attack[60,61]. ICS, inhaled corticosteroid, TARC, thymus activation regulated cytokine; TSLP, thymic stromal lymphopoietin.~~Fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophil measurements yield distinct information on this biological process.~~

~~Figure 3~~FIGURE 3

A suggested algorithm for assessing and managing patients with severe asthma. * = Adherence (*e.g.* ≥ 75% prescription pick-up rate; see Table 2) is ideally assessed in every new patient, but must certainly be confirmed prior to biological prescription; # = biomarker high, *i.e.* blood eosinophil cell counts ≥0.~~3~~315 ~~×~~10^9 cells/~~per~~ L and/or fractional exhaled nitric oxide ≥~~50~~ 25 ppb; † = usually a combination of long-acting bronchodilator/low-dose inhaled corticosteroid (ICS) plus a long-acting muscarinic; ACQ = asthma-control questionnaire; IgE = immunoglobulin E; MART = maintenance and reliever therapy. ACQ = asthma-control questionnaire; IgE = immunoglobulin E.

TABLE 1: 'Must be asked' elements on clinical history in suspected severe asthma

Etiology and contributing factors
Occupation and exposure history
Household pets, dusty or moldy environments
Known allergies, associated symptoms ± confirmatory testing
Aspirin/COX-1 inhibitor sensitivity
Smoking and vaping history
Illicit inhaled drug use: smoked, snorted or vaporized
Pregnancy
Psychosocial stressors
Asthma & asthma attack history
Age of asthma onset, method of diagnosis
Previous intensive care / intubation for asthma
Number of asthma attacks requiring corticosteroids and/or hospital admissions
Number of lower respiratory tract infections requiring antibiotics
Usual triggers and symptoms of attacks
Current asthma control (*e.g.* ACQ, ACT, or GINA control checklist)
Response to systemic corticosteroids: significant and prompt response suggests eosinophilic airway pathology
Current and previous asthma therapies
Current treatment regimen, including over-the-counter medications
Controller and reliever therapies felt to be helpful – pattern of use and response
Controller and reliever therapies felt to be unhelpful – previous treatment failures
Barriers to treatment adherence
Vaccination history

Comorbidity assessment
Cardiovascular and metabolic comorbidities; ischemic heart disease, diabetes, (…)
Common type-2-high comorbidities: especially nose, sinus and skin disease
Common type-2-unrelated comorbidities: anxiety/depression, recurrent chest infections, gastroesophageal reflux disease, (…)
Common respiratory red flags and/or symptoms of 'asthma plus' conditions: ABPA, CEP, EGPA, (…)

ABPA = allergic bronchopulmonary aspergillosis, ACQ = asthma control questionnaire, ACT = asthma control test, CEP = chronic eosinophilic pneumonia, EGPA = eosinophilic granulomatosis with polyangiitis, GINA = global initiative for asthma

TABLE 2. Methods used to assess treatment adherence in severe asthma

Method	Association with outcomes	Logistics	Comments
Prescription records	Solid evidence that patients with low consumption of ICS do less well	Simple in most health care systems	Does not assess treatment use directly. Accurate information not always available.
Blood drug levels	Has not been associated with clinical outcomes	Widely available	Only applicable for theophylline and prednisolone. Undetectable prednisolone and / or normal serum cortisol generally accepted as a reliable marker of non-adherence to maintenance prednisolone.
FeNO suppression test[24,25]	Significant suppression of FeNO after 7 to 28-day monitored ICS therapy is associated with longer-term response to supervised treatment	Difficult to carry out in most healthcare systems	Some patients better understand the positive impact of ICS treatment by seeing a measurable decrease in their airway inflammation matching their clinical improvement.
Remote monitoring of chipped inhaler devices[28]	Allows real-time monitoring of adherence to asthma treatments May improve adherence and decrease exacerbations in research settings	'Smart Chipped inhaler' technology varies with inhaler type	Increasingly carried out in severe asthma clinics. Technology and wireless communication capacities rapidly evolving.

FeNO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid.

TABLE 3: Biomarkers of Type-2 Airway Inflammation

Biomarker	Cut-offs	Association with treatment response	Comments
IgE	Variable	Anti-IgE	IgE levels do not consistently predict clinical outcomes nor treatment responsiveness
Blood eosinophil count	≥ 0.153 $\times 10^9$ per L	Corticosteroids Anti-IL-5/5R Anti-IL4Rα Anti-IgE Anti-TSLP	Generally available, cheap, directly relates to asthma control and risk of asthma attacks
Sputum eosinophils	≥> 2-3%	Corticosteroids Anti-IL-5 Anti-IL4Rα	Not routinely available, tissue specific, time-consuming
FeNO	≥25 ppb	ICS Anti-IL-4Rα Anti-TSLP	Quick, cheap, non-invasive, associated with increased risk of asthma attacks; increases probability of ICS-responsiveness

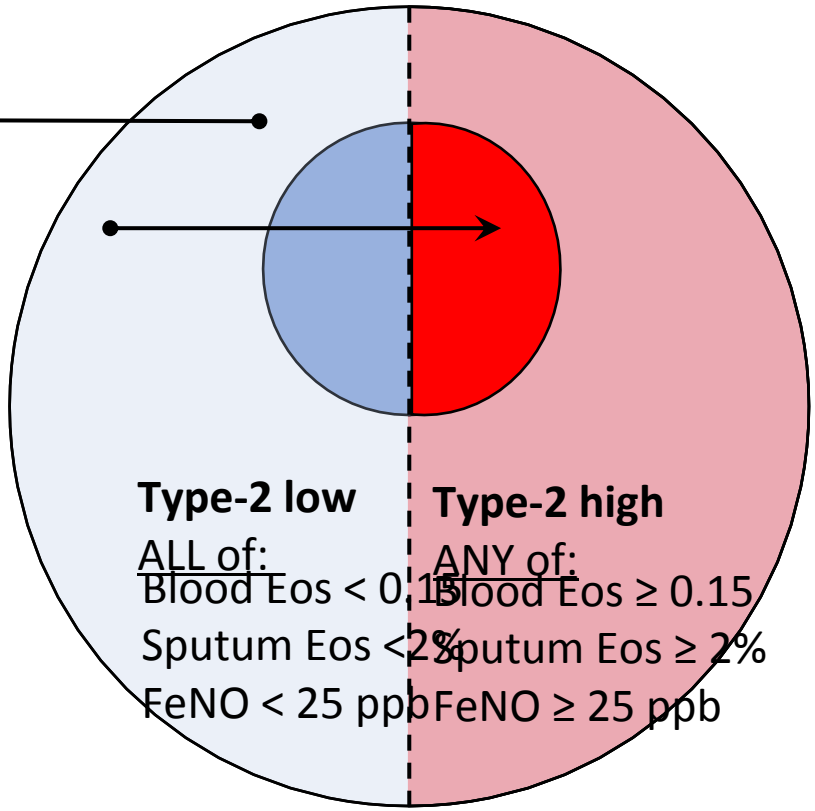
FeNO = fractional exhaled nitric oxide, ICS = inhaled corticosteroid, Ig = immunoglobulin, IL = interleukin, R = receptor. TSLP = thymic stromal lymphopoietin. Modified from Ref reference 14.

TABLE 4: Suspected contributing factors to severe asthma and their investigations

Suspected problem	Possible investigation
Bronchiectasis, emphysema, large airway pathology	High-resolution chest CT (inspiratory and expiratory images) ± bronchoscopy
Chronic airways infection	Sputum cultures (×2), including for acid-fast bacilli; ± bronchoscopy
Chronic rhinosinusitis with nasal polyposis	Sinus CT ± nasoendoscopy / ENT referral
Corticosteroid-induced side effects	Specific to target organ, but may include: glycosylated hemoglobin, blood pressure monitoring, 8 a.m. cortisol, bone density measurement, ophthalmologist referral
Cystic fibrosis	Sweat chloride ± genetic testing
Dysfunctional breathing pattern*	Respiratory physiotherapy assessment
Dyspepsia, GERD#	GI referral for esophageal manometry, pH monitoring and/or endoscopy
Helminth infection	Specific to travel history, but may include: stool microscopy exam for parasitic ova and larvae, *Stronglyoides* and/or *Schistosomiasis* serology
Hypereosinophilic syndromes	Hematology referral for cytogenetics (FIP1L1/PDGFRA) and/or further testing[55]
Immunodeficiency	IgG, IgM, IgA ± immunology referral
Inducible laryngeal obstruction	ENT / speech and language therapy with dynamic laryngoscopy
Obstructive sleep apnea or other sleep disordered breathing	Sleep study
Unexplained breathlessness	Echocardiogram and full pulmonary function tests ± CPET
Vasculitis	Anti-neutrophil cytoplasmic antibodies ± affected tissue (*e.g.* skin, nose, nerve or lung) biopsy

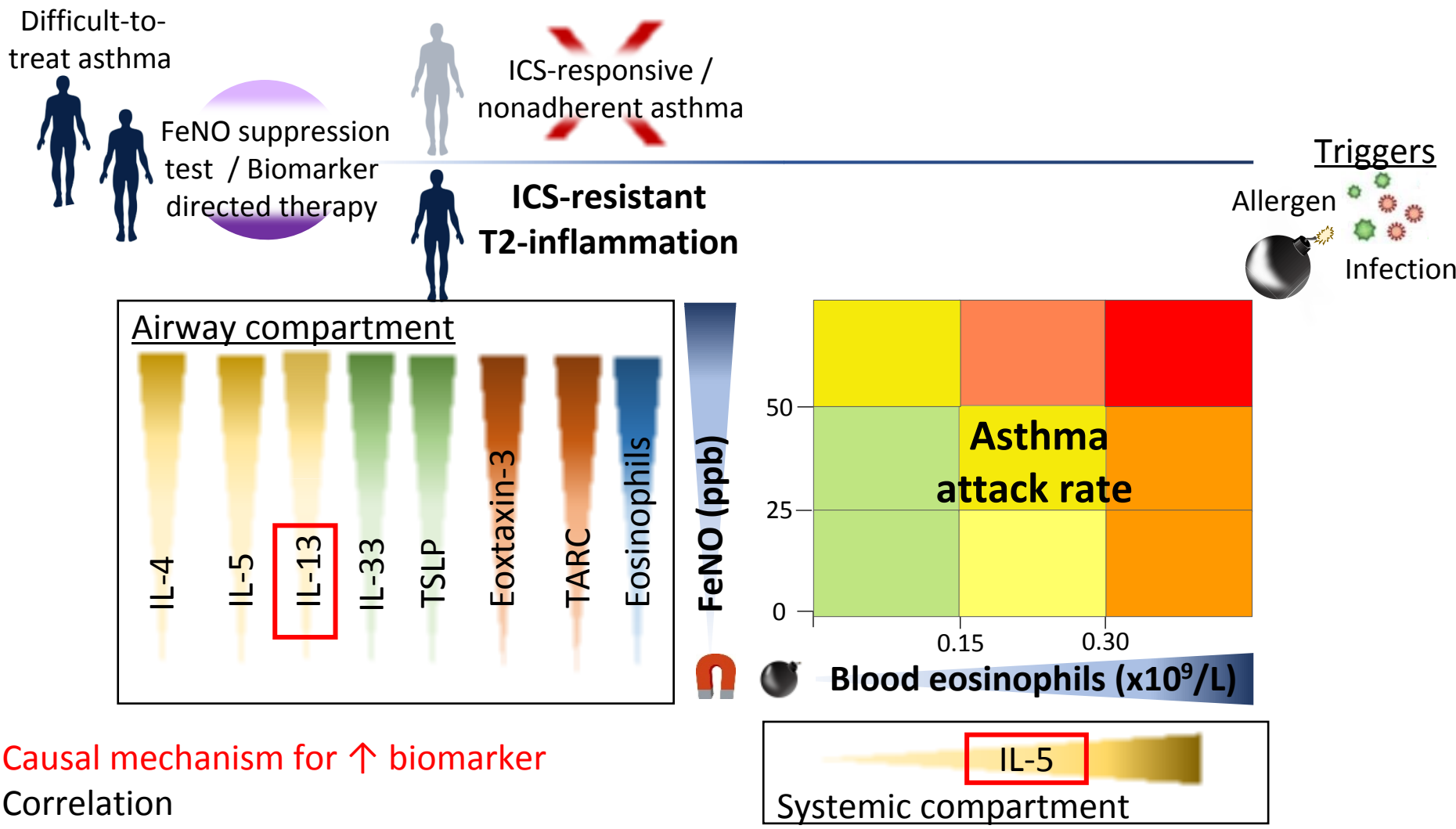
* In cases where dysfunctional breathing overlaps with persistent type-2 inflammation, the latter entity can be treated in parallel; #Gastro-esophageal reflux disease (GERD) investigation and treatment is unlikely to result in improved asthma control[54]. CF = cystic fibrosis, CPET = cardiopulmonary exercise testing, CT = computed tomography, ENT = ear-nose-throat surgery, Ig = immunoglobulin, SALT = speech and language therapy.

'Difficult Asthma'
GINA Step 4-5 treatment
+ Uncontrolled asthma



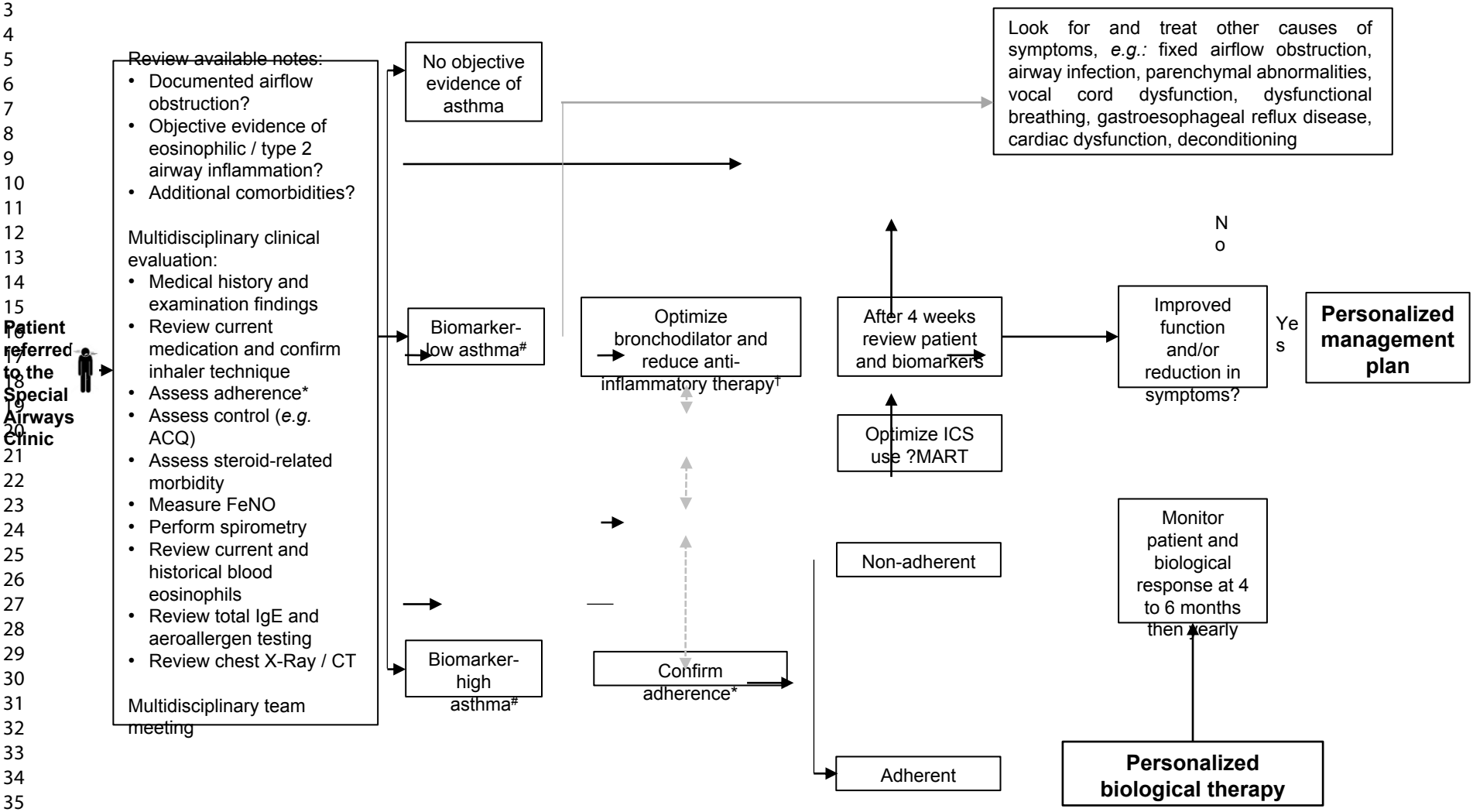
Severe Asthma
Asthma diagnosis confirmed
+ Contributory factors optimized:
- GINA Step 4-5 treatment
- Good inhaler technique
- Good adherence

+ Uncontrolled Asthma
- Frequent (≥ 2) severe asthma attacks in the previous year
- ACQ score > 1.5



Causal mechanism for ↑ biomarker

Correlation


Patient referred to the Special Airways Clinic
Review available notes:
• Documented airflow obstruction?
• Objective evidence of eosinophilic / type 2 airway inflammation?
• Additional comorbidities?
Multidisciplinary clinical evaluation:
• Medical history and examination findings
• Review current medication and confirm inhaler technique
• Assess adherence*
• Assess control (e.g. ACQ)
• Assess steroid-related morbidity
• Measure FeNO
• Perform spirometry
• Review current and historical blood eosinophils
• Review total IgE and aeroallergen testing
• Review chest X-Ray / CT
Multidisciplinary team meeting
No objective evidence of asthma
Look for and treat other causes of symptoms, e.g.: fixed airflow obstruction, airway infection, parenchymal abnormalities, vocal cord dysfunction, dysfunctional breathing, gastroesophageal reflux disease, cardiac dysfunction, deconditioning
Biomarker-low asthma#
Optimize bronchodilator and reduce anti-inflammatory therapy†
After 4 weeks review patient and biomarkers
Improved function and/or reduction in symptoms?
No
Yes
Personalized management plan
Optimize ICS use ?MART
Biomarker-high asthma#
Confirm adherence*
Non-adherent
Monitor patient and biological response at 4 to 6 months then yearly
Adherent
Personalized biological therapy