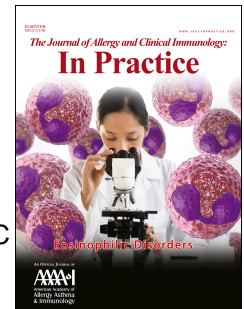


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Difficult-To-Control Asthma Management In Adults

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36 Kinaset.

37 **List of keywords**

38 Severe asthma, systematic assessment, endotyping, biologics

39

40 **List of abbreviations**

41 BT Bronchial thermoplasty

42 FeNO Fraction of Exhaled Nitric Oxide

43 FEV₁ Forced Expiratory Volume in one second

44 GINA Global Initiative for Asthma

45 GERD Gastro esophageal reflux disease

46 ICS Inhaled Corticosteroid

47 IL Interleukin

48 KIT KIT proto-oncogene receptor tyrosine kinase

49 LABA Long-acting beta agonist

50 LAMA Long acting anti-muscarinic

51 MDT Multi-Disciplinary Team

52 NAEPP National Asthma Education and Prevention Program

53 T2 Type 2

54

55 Abstract (189/200 words)

56 The management of difficult to control asthma remains a significant challenge, which
57 frequently requires the input of the wider multi-disciplinary team. This review will cover the
58 importance of systematic assessment, phenotyping, treatment options at step 4, an
59 overview of biologics and novel therapies for Type 2 inflammation, and non-pharmacologic
60 interventions.

61 Once people have been identified as suffering from difficult to control asthma it is
62 important to use the systematic assessment process to allow accurate diagnosis and
63 optimisation of adherence as well as identification and treatment of any relevant
64 comorbidities.

65 Before initiating a biologic, it is important to optimise inhaled therapies and sufficiently
66 phenotype individual patients to allow for the logical use of biologic agents targeting type 2
67 inflammation. For patients that either do not have evidence of type 2 inflammation or
68 remain symptomatic despite biologics, attention should be paid to the available non-
69 pharmacological interventions.

70 Difficult to treat asthma remains an area of significant unmet need, but improvements in
71 models of service delivery and the ongoing pharmacological pipeline are causes for
72 significant optimism that sooner rather than later there will no longer be asthmatic patients
73 who are difficult to treat

74

Introduction

Asthma remains the most common chronic respiratory disease, affecting more than 300 million individuals worldwide [1]. For the majority of people, it is well controlled with currently available therapies provided that there is an adequate focus on medicine optimisation, including inhaler technique, in combination with appropriate health care provider and patient education that reinforces the routine use of peak flow monitoring and personalised asthma action plans. A significant minority of people have difficult to control asthma. This heterogeneous group includes people with truly severe refractory asthma as well as people with either poor adherence to prescribed therapies, significant contributing comorbidities, and even people whose symptoms are not due to asthma at all. This review will focus on the patient journey from systematically assessing people with difficult to treat asthma to allow for accurate phenotyping and the identification of comorbidities to treatment options recommended at NAEPP (National Asthma Education Prevention Program) and Global Initiative for Asthma (GINA) Step 4 as well as the addition of biologics or other targeted pharmacological therapies and non-pharmacological interventions recommended at Step 5 (GINA) or Steps 5 and 6 (NAEPP).

The definition of difficult to treat versus severe asthma

Over the years multiple definitions of severe asthma have been generated and tend to be based on asthma control or medication burden. There is now consensus around the terminology of difficult to treat and severe asthma [2]. The term 'difficult to treat' asthma can be applied to any patient who remains poorly controlled despite being prescribed at least NAEPP or GINA) step 4 therapy (1). This intentionally broad definition simply means that patients have ongoing symptoms, for whatever reason and have been prescribed high

intensity asthma therapy (e.g. inhaled corticosteroids and long acting beta agonists (ICS/LABA)) by their health care provider. Only a percentage of people with difficult to treat asthma fulfil the far more rigorous definition of 'severe asthma'. There have been several definitions of severe asthma, but the European Respiratory Society/American Thoracic Society taskforce definition first suggested by Chung and colleagues in 2014 (2) has been universally adopted. This definition recognises the need to confirm the diagnosis of asthma as well as adherence to treatment in combination with either NAEPP or GINA step 5 or 6 treatment to prevent asthma from becoming uncontrolled or which remains uncontrolled despite this therapy; in this context, poor control is defined in terms of asthma exacerbations, poor symptom control, or lung function.

The prevalence of difficult to treat and severe asthma has been best investigated by Hekking et al (3) who used a combination of automated pharmacy dispensing records, a questionnaire to assess correct diagnosis and asthma control, and, for adherence, an assessment of prescription filling and inhaler technique review in a representative sample of Dutch patients. Hekking found that 24% of asthmatics were on high intensity treatment with 17% fulfilling the definition of difficult to treat asthma and 3.7% suffering from severe asthma.

The causes of difficult to treat asthma

There are many causes for ongoing symptoms in people with difficult to treat asthma beyond severe asthma per se, and often they are multifactorial in a single individual. The causes can be broken down into those due to ongoing asthma, which may either be due to non-adherence or undertreatment, the impact of comorbidities, including those induced

by systemic corticosteroids, or the presence of either an asthma mimic or another disease that has been misdiagnosed as asthma.

Non-adherence occurs across the spectrum of asthma severity and is frequently non-intentional due to poor inhaler technique (4) . Nearly half of difficult to treat asthmatics may have suboptimal adherence to preventer medications.(5). The impact of adherence on difficult to control asthma is reviewed in detail in a companion article in this issue [8]. The majority of patients with severe asthma will have poorly controlled disease with ongoing symptoms and are at increased risk of an exacerbation requiring treatment escalation. For many with difficult to treat asthma, the combination of multimorbidity due to the underlying disease process, e.g. chronic rhinosinusitis with nasal polyps in patients with eosinophilic asthma, and the consequences of systemic corticosteroids, e.g. weight gain and gastro-esophageal reflux disease (GERD), drive the symptom burden (6). Many comorbidities should be considered when assessing patients with severe asthma including allergic rhinoconjunctivitis, chronic rhinosinusitis with nasal polyps, breathing pattern dysfunction, inducible laryngeal obstruction, GERD, psychosocial factors, physical deconditioning, obesity and obstructive sleep apnoea (6). The role of co-morbidities in patients with difficult to treat asthma is discussed in detail in a companion article in this issue (10)

Asthma is both common and challenging to diagnose. This can lead to symptomatic patients being labelled with asthma, and, when they do not respond to therapy quickly, being labelled as having difficult to treat asthma. Up to 12% of specialist-referred asthmatics undergoing systematic assessment later have the diagnosis withdrawn (7), reinforcing the

requirement for early and accurate diagnosis using objective tests of airways inflammation and physiology. Several conditions, frequently referred to as components of the pulmonary eosinophilic syndrome, can mimic asthma. Given the presentation with breathlessness, wheeze and evidence of eosinophilia, it is not surprising that eosinophilic granulomatosis with polyangiitis, chronic eosinophilic pneumonia, and allergic bronchopulmonary aspergillosis are frequently initially diagnosed as severe asthma (6). Understandably other respiratory pathology that presents with airways obstruction such as chronic obstructive pulmonary disease and bronchiectasis are also misdiagnosed as severe asthma (7).

Systematic assessment

Since the majority of people with difficult to treat asthma do not have severe asthma, it is logical to systematically assess patients before escalating to biologics or other treatment options. Conventionally the idea of the systematic assessment is to consistently answer the following questions: 1. Does this patient have asthma? 2. Are they adherent with their prescribed therapy? 3. Is asthma the cause of their current symptoms? The systematic assessment should also include an assessment for the presence of comorbidities and the impact of systemic corticosteroids on the patient.

There is no universally agreed upon way to perform a systematic assessment, but it is helpful for it to be based within a multidisciplinary team (MDT) to ensure that a holistic approach is taken, which consistently answers the key questions to differentiate difficult to treat from severe asthma (8). The assessment should include review by a specialist in severe asthma and input as required from members of the MDT, which can include nurse specialists, physiotherapists, pharmacists, allergists, rhinologists, gastroenterologists and

voice therapists. Objective testing to demonstrate airways obstruction, inflammation and/or hyperreactivity is mandatory, and imaging is often required to identify or exclude other pathologies (7). Lastly, in this era of precision medicine, it is important to understand what type of asthma each patient has and the individual's endotype; this can be facilitated by measurement of blood or sputum eosinophils, exhaled nitric oxide, and serum IgE. The programmed set of investigations frequently includes blood testing to exclude other disease processes, confirm atopy, and measure adherence to oral therapies (7). Laryngoscopy, tailored barium swallow, and esophagram can be utilized to identify various comorbidities. In some circumstances bronchoscopy can be performed to evaluate the upper and lower airways and to identify other causes of airflow obstruction (e.g airway tumour or large airways collapse with symptoms), evidence of infection, or airway eosinophilia.

Given the intensive input required to perform a systematic assessment it is important to note that multiple studies have now demonstrated the utility of systematic assessment in improving outcomes. Gibeon et al reported that patients who had undergone systematic assessment at severe asthma centres in the UK had fewer exacerbations and unscheduled healthcare utilisation in combination with improved asthma control (9), and these results have been replicated in other healthcare settings (10).

Treatment options at Step 4 and above

Patients that do meet the benchmarks for uncontrolled severe asthma, typically qualify for Step 4 (or above) in the GINA (1) or the NAEPP Guidelines (11). There has long been broad agreement between both sets of guidelines that the "background" recommended controller therapy in persistently uncontrolled more severe asthma is medium to high doses of inhaled

corticosteroids with a concurrent long-acting beta-agonist, typically in a combination product inhaler. The most recent version of both guidelines (GINA 2021 and NAEPP Focused Update 2020) embrace the concept of maintenance ICS/LABA with as needed ICS-formoterol used as the reliever inhaler (Maintenance and Reliever Therapy). The preferred option at Step 4 is medium dose ICS-formoterol with as needed ICS-formoterol. It is important to understand that this relates to medium-high doses of ICS, depending on the intensity of “reliever” puffs of ICS-formoterol being used – a “medium-plus” level of ICS. At Step 5, both guidelines favour the addition of a long acting anti-muscarinic (LAMA) and/or the escalation to high dose ICS/LABA, the latter important in patients who continue to have exacerbations (although the GINA guidelines suggest continued use of low dose ICS/formoterol as the reliever inhaler in Step 5).

The recommendation to consider the addition of a LAMA prior to escalating to high dose ICS is appealing as a steroid sparing strategy. It is important to understand, however, that this recommendation is based on clinical trials that included subjects with an abnormal pre-bronchodilator forced expiratory volume in one second (FEV₁) (typically < 85% predicted), and only some required high doses of background ICS/LABA or an exacerbation history. Thus, they may not be representative of severe asthma patients by the aforementioned definition. The study by Lee et al did include 33% of subjects on high dose ICS/LABA with a history of an episode of poor asthma control in the past year as well as an abnormal pre-bronchodilator FEV₁ between 30-85% predicted, but all were stepped down to medium dose ICS/LABA during the run-in and presumably did not exacerbate, suggesting they were at the less severe end of the spectrum (12). Subjects were randomized to multiple arms defined by the ICS/LABA dose (medium or high ICS/LABA) with or without the addition of a

LAMA. Overall, the groups randomized to add-on LAMA had improved symptoms and lung function, but asthma exacerbations were reduced in the group randomized to the higher dose ICS. As such, LAMA therapy might be most effective in patients with the clinical trait of lower lung function that is reminiscent of COPD, for which these drugs have been FDA approved, and it is unclear whether they would be as effective in patients with frequent exacerbations.

Macrolide therapy is another example of a medication re-purposed from a different obstructive lung disease (bronchiectasis) being used as a potential controller in more severe asthma patients. The incidence of bronchiectasis on CT scan imaging in asthma has been reported in 19-40% of severe asthma patients and this feature is associated with poorer lung function (13). Several studies have shown decreased exacerbation rates in patients with obstructive lung diseases (bronchiectasis, COPD, and asthma), treated with macrolides, with some studies reporting a greater reduction in those with coexisting eosinophilic airway inflammation, fungal sensitization, or colonization with pseudomonas (14). The decrease in exacerbation rate in these related but different obstructive diseases suggests that macrolides have diverse anti-inflammatory and antibiotic effects and that the subgroup of asthmatics with features of these other two diseases (bronchiectasis or COPD) might be a better responder group for this potential add-on controller.

Taken together, the above discussion on the use of LAMAs and chronic macrolide therapy in uncontrolled asthma supports the concept that precision medicine approaches based on clinical characteristics (treatable traits) need to be much earlier in our treatment algorithms. Figure 1 illustrates a working conceptual basis by which to potentially direct a precision

medicine approach to the use of LAMAs and macrolides in uncontrolled severe asthma, prior to the biologic immunomodulator space.

If asthma remains uncontrolled after escalation to high dose ICS/LABA and a trial of LAMA and/or chronic macrolide, it is time to consider treatment with a biologic immunomodulator, and disease phenotyping with biomarker assessment is vital. The pivotal clinical trials for the biologic immunomodulators have been exclusively limited to severe asthma patients on background high dose ICS/LABA therapy with frequent asthma exacerbations and required very specific biomarkers. These trials are the result of more than two decades of research into pathobiologic mechanisms in severe asthma leading to the concept of target driven immune modulation, and, thus, the appropriate use of these medications is dependent on the ability to identify specific phenotypes of asthma characterized by specific biomarkers to guide therapy.

Phenotypes of Severe Asthma

Phenotyping of a complex disease such as asthma progressed when machine learning unbiased modelling techniques, such as cluster analyses, replaced the categorization of patients as mild, moderate or severe. The latter approach worked well for guideline-based assessment of disease control and recommendation for initial therapy, but marked disease heterogeneity in severe asthma became apparent over the years leading to a transition to the concept of disease phenotypes. Research-oriented severe asthma cohorts, registry-driven cohorts, and country-specific cohorts have collected a wide array of data ranging from clinical characteristics to lung function and biomarker measurements (15) . Using

modelling efforts, these cohorts have identified multidimensional clinical asthma phenotypes that resemble the patients we see in clinic.

Most of the cohorts coalesce around three common clinical phenotypes of severe asthma that are well demonstrated by the original Severe Asthma Research Program (SARP) “cluster” phenotypes shown in Figure 2 (15). SARP Cluster 4 is representative of “traditional” childhood onset, long-duration, allergic asthma. This group is the most atopic, and the majority have evidence of blood and sputum eosinophilia. Patients in SARP Cluster 5 have later onset (early adulthood), long-duration, less allergic asthma with poor lung function and chronic airflow obstruction. This is the most severe asthma cluster with high exacerbation rates, frequent steroid dependence, and many co-morbidities. Only a subgroup of Cluster 5 has elevated blood or sputum eosinophils. SARP Cluster 3 is characterized by a group of obese women with adult-onset eosinophilic asthma and coexisting severe chronic rhinosinusitis frequently requiring surgery. This group tends to be very steroid responsive, having frequent asthma exacerbations but rarely requiring emergency room or inpatient health care utilization, presumably because they improve rapidly with steroids. Ideally, these clinical phenotypes would be tightly correlated with disease biomarkers that would allow precision therapeutic approaches, but biomarker heterogeneity exists within each clinical phenotype (16).

The four biomarkers that have been studied extensively in asthma are blood and sputum eosinophils, total IgE (as an imprecise and low sensitivity marker of atopy), and fractional excretion of nitric oxide (FeNO). They are all correlated, but not perfectly so, suggesting they all measure slightly different but complementary aspects of airway eosinophilia and

atopy. These Type 2 (T2) biomarkers are present in many of the severe asthma subjects in each of the above clinical asthma phenotypes and are not specific for any given SARP phenotype (Figure 2). Thus, biomarkers identify which biologic mechanisms may be important in a given patient and which immunomodulator would be indicated to alter this pathobiology. While the presence of these biomarkers identify patients who are likely to respond to T2 targeted therapy, they do not distinguish which “T2 high” biologic that patient is most likely to respond to (17). Clinicians who treat many patients with asthma biologic immunomodulators still take their “best guess”, but most would anecdotally agree that the response to a given biologic seems different in the described clinical phenotypes, but we are not at that level of precision yet.

Biologic choice

Over the last two decades, asthma management has evolved beyond standardized inhaler regimens with ICS/LABA, and the era of precision medicine has resulted in introduction of targeted biologic therapies that have revolutionized treatment for patients with severe asthma. Anti-IgE therapy with omalizumab was the first such therapy approved in the early 2000’s and resulted in significant reduction in exacerbations in patients with allergic asthma(18). It has recently been approved for nasal polyps as well. Since 2015, therapies targeting interleukin (IL) 5 (mepolizumab, reslizumab) or its receptor (benralizumab) have resulted in significant benefits in patients with eosinophilic asthma, reducing exacerbations and improving lung function and asthma related quality of life (19). Mepolizumab and benralizumab have also been shown to facilitate corticosteroid withdrawal in patients dependent on oral corticosteroids (20), and mepolizumab has also been approved for the condition of eosinophilic granulomatosis with polyangiitis(21) and for rhinosinusitis with

nasal polyposis. Most recently, the anti-IL-4/13 therapy dupilumab has shown benefits in patients with type 2 asthma and in oral corticosteroid dependent patients, reducing exacerbations, improving lung function, and improving asthma related quality of life (22, 23). Dupilumab has also been approved for atopic dermatitis and chronic sinusitis with nasal polyps. All of these therapies have a good safety profiles, and they have also been shown to have sustained efficacy over the long term(24).

Since there have been no direct head-to-head studies evaluating these biologics for type 2 severe asthma patients, a major challenge for providers is how to choose between these agents. This topic is discussed in a companion article in this issue (36). Briefly, for some individuals with a dominant biomarker (e.g eosinophilia or high FeNO), or specific T2 comorbidities (e.g. atopic dermatitis, chronic urticaria, or chronic rhinosinusitis with nasal polyps), certain agents may have greater efficacy than others. However, as many patients have mixed/overlapping T2 phenotypes, all available options are often reasonable and offer some efficacy. Given the heterogeneity and dynamic nature of asthma pathophysiology, there is no single biologic agent that will be universally effective for all severe asthma patients, and drug costs (and potential safety concerns) usually prohibit use of combinations of biologics.

Currently available biologics target patients with a T2 phenotype. While studies targeting non T2 pathway cytokines such as IL-17 (25) and IL-23 (26) have produced negative results, it is hoped that targeting upstream cytokines such as thymic stromal lymphopoietin (27) or IL-33 (28) will offer additional benefits, as these therapies have the potential to address multiple mechanisms of disease, including non-eosinophilic asthma.

Non biologic therapies

Whilst biologic therapies have been increasingly used to help patients with severe asthma, nonbiologic strategies have also benefited patients. Macrolide therapy in severe asthma is reviewed earlier in this article. As benefits were observed in both eosinophilic and non-eosinophilic asthma and as its cost is significantly lower than that of the biologics, azithromycin serves as a useful add-on therapy for many patients with persistent asthma.

KIT proto-oncogene receptor tyrosine kinase (KIT) is found on mast cells, is essential for mast cell development and survival, and has become a target for T2-low asthma as serum KIT levels correlate with asthma severity. Imatinib is a tyrosine-kinase inhibitor known for its use in chronic myeloid leukaemia. Cahill et al (29) enrolled 62 poorly controlled asthmatics with airway hyper-responsiveness in a randomized, double-blind, placebo-controlled trial which demonstrated a significant improvement in airway hyperresponsiveness to methacholine and a significant reduction in serum tryptase with imatinib compared to placebo. Imatinib is now being studied prospectively as part of the Precision interventions in the Severe/exacerbating (Precise) Asthma network (30).

Other oral therapies that target the prostaglandin D2 receptor have been evaluated, but, unfortunately, have yielded inconsistent results (31) and are not being developed further. Dexamipexole has produced a reduction in blood eosinophils (32) and is actively being investigated as a novel oral anti-eosinophilic in people with asthma.

Bronchial thermoplasty (BT) is a unique intervention involving radiofrequency thermal ablation and has the potential to reduce airway smooth muscle mass. It has been successfully used in selected patients whose clinical symptoms and airway smooth muscle hypertrophy are poorly responsive to conventional treatments and who demonstrate a lack of significant contraindications to BT, such as life-threatening asthma, recent intensive care unit admission, or implantable electronic device. The AIR2 Trial demonstrated the

effectiveness and safety of bronchial thermoplasty in treatment of uncontrolled severe asthma, using a sham-controlled double-blinded design (33) . Five-year follow up of treated patients demonstrated a sustained reduction in severe exacerbations and emergency department visits and has suggested no long-term safety issues (46). However, when to use BT remains unclear, and all major guidelines have recommended that BT only be considered in the context of clinical trials or registries.

Non-pharmacological interventions

Whilst pharmacologic approaches remain the mainstay of therapy for severe asthma, several non-pharmacologic interventions are available as adjunct therapies to inhalers and biologics for these challenging patients. Use of breathing techniques, inspiratory muscle training, management of anxiety, Vitamin D supplementation, and tailored pulmonary rehabilitation programs should be considered as components of the comprehensive approach to severe asthma. Most, if not all, of these interventions have a favourable side effect profile and may improve quality of life, symptom management and possibly reduced healthcare use as a consequence. Current GINA guidelines (1) also emphasize physical activity, a healthy diet, smoking cessation, weight reduction, and avoidance of environmental tobacco smoke, occupational exposures, and medications that can make asthma worse (e.g. aspirin , beta blockers).

Conclusions

Advances in our understanding of severe asthma over the last two decades have revolutionized the way that we approach patients with severe asthma. A greater appreciation of the heterogeneity and dynamic nature of severe asthma and of the multiple

386 pathways involved has resulted in increased utilization of phenotyping and endotyping,
387 which has led to a more precision-based approach for our patients. While targeted
388 monoclonal antibodies has significantly improved outcomes, other strategies including use
389 of macrolide antibiotics and non-pharmacologic approaches, have also benefited this group
390 of patients who have significant unmet need. As we gain more insights into disease
391 pathophysiology, it is expected that future therapies will have an even greater impact in this
392 difficult to treat population.

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Figure Legends:

Figure 1. Evaluation and management of severe asthma in the pre-biologic space. The yellow triangle represents the continuum of clinical traits in the two of the three obstructive lung diseases (bronchiectasis and COPD) which can co-exist with asthma. Starting at the left lower corner of the triangle where high dose ICS/LABA is not controlling asthma, clinical assessments of chronic airflow obstruction and bronchiectasis features direct add-on therapy with “re-purposed drugs” such as LAMAs and/or macrolides. If patient do not possess these 2 traits, or have not responded, phenotypic and biomarker guided therapy should be considered.

Figure 2. Summary of clinical characteristics and biomarkers in the three severe asthma clinical phenotypes identified in the original SARP cluster analysis (age 12 and older).(19)

Table 1- Therapies for Difficult to control asthma beyond ICS/LABA/LAMA

Currently available Biologics

Anti-IgE	Omalizumab
Anti-IL5	Mepolizumab, Reslizumab
Anti-IL5-receptor	Benralizumab
Anti-IL4/IL13	Dupilumab

Future Biologics

Anti-TSLP	Tezepelumab
Anti-IL33	Itepekimab
Long Acting anti-IL5 receptor	Depemokimab

Non-Biologic therapies

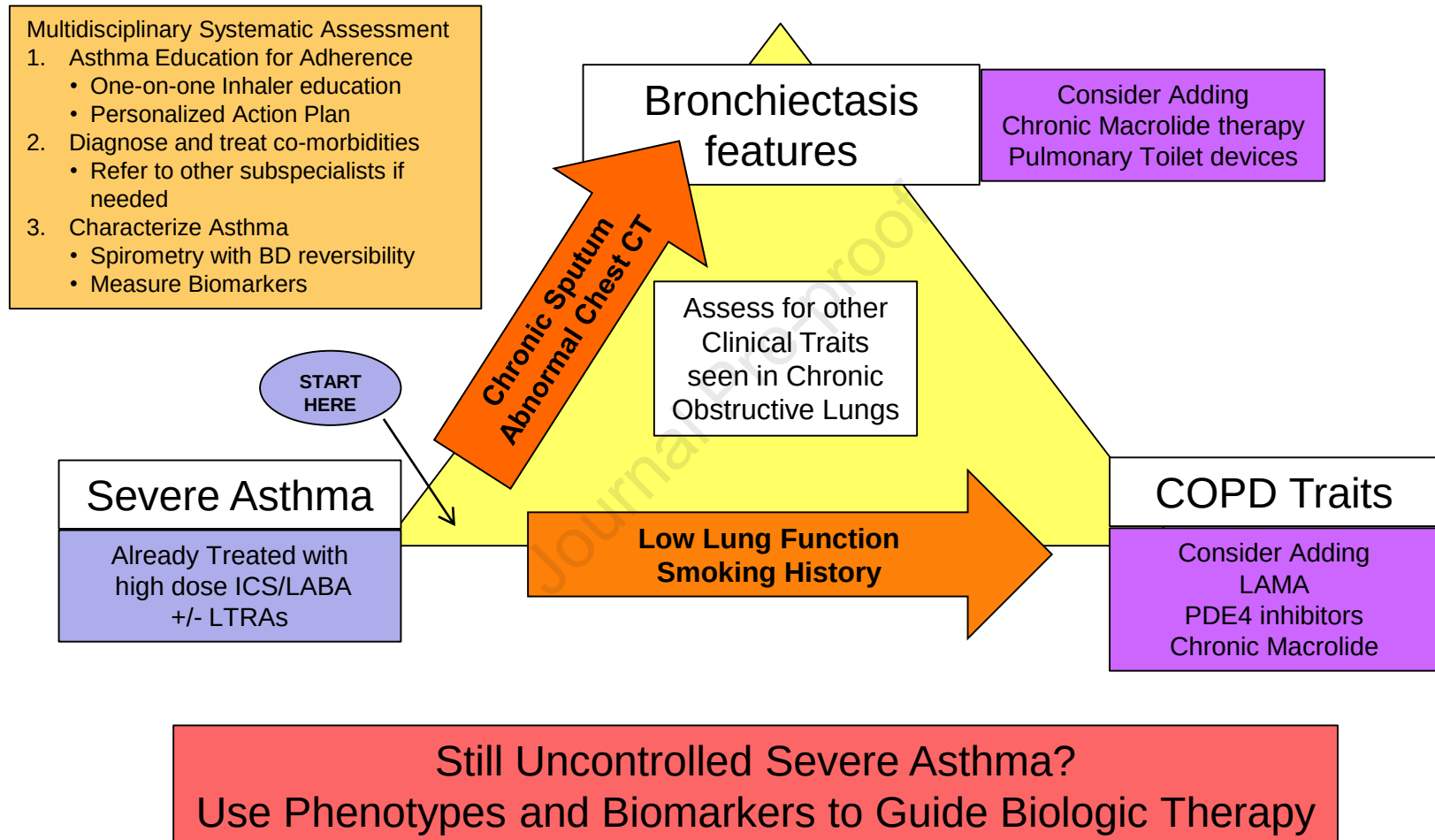
Macrolide Antibiotics	Azithromycin
Bronchial Thermoplasty	

Other therapies in development

Kit inhibitor	Imatinib
Prostaglandin D2 Inhibitor	Fevipirant, GB001
Dexramipexole	

Nonpharmacologic strategies

Breathing techniques
 Inspiratory muscle training
 Management of anxiety
 Vitamin D supplementation
 Pulmonary rehabilitation programs



SARP CLUSTER 4 CHILDHOOD ONSET SEVERE ALLERGIC ASTHMA	SARP CLUSTER 3 OBESE ADULT ONSET ASTHMA with RHINOSINUSITIS	SARP CLUSTER 5 SEVERE ASTHMA with PERSISTENT AIRFLOW LIMITATION
Childhood Onset (<18) Long duration Frequent exacerbations with 24% reporting hospitalizations 36% chronic oral steroids Abnormal FEV1, but reverses to near normal Comorbidities • 40% Chronic sinus disease • 24% nasal polyps • 83% atopic by Skin testing • 48% Blood Eos ≥ 300 • 54% Sputum Eos $\geq 2\%$	Adult Onset (40s) Short duration 58% Obese Frequent exacerbations managed as outpatient OCS Near Normal FEV1 Comorbidities • 63% Chronic sinus disease • 19% Nasal Polyps • 64% atopic by Skin testing • 36% Blood Eos ≥ 300 • 48% Sputum Eos $\geq 2\%$	Adolescent Onset (20s) Long duration Frequent exacerbations with 28% reporting hospitalizations 47% chronic oral steroids Very poor FEV1, does not reverse to normal Comorbidities • 53% Chronic sinus disease • 25% nasal polyps • 66% atopic by Skin testing • 44% Blood Eos ≥ 300 • 34% Sputum Eos $\geq 2\%$