

## PATIENTS WITH SEVERE ASTHMA NEED ACCURATE DIAGNOSIS AND CORRECT TREATMENT: HOW CAN WE ACHIEVE THAT?

Dr Chan Kwok Wai Adrian

### ABSTRACT

Since asthma is frequently encountered in the primary care setting, it is important to distinguish uncontrolled or difficult-to-control asthma from severe asthma. Severe asthma is defined as asthma that is uncontrolled despite adherence with an optimised high-dose combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) therapy, or that requires high-dose ICS-LABA to remain controlled. This article highlights simple decisions and diagnosis steps that may help primary care physicians and general practitioners to identify patients who could benefit from tertiary care specialist assessment once other factors, such as inhaler technique, adherence, and comorbidities have been evaluated. It also briefly discusses the impact of oral corticosteroids (OCS) use and the challenges of the COVID-19 lockdown on asthma management.

**Keywords:** asthma, COVID-19, inhaled corticosteroids, oral corticosteroids, referral, primary care, diagnosis

SFP2021; 47(7) : 12-15

### DIFFERENTIATING DIFFICULT-TO-TREAT FROM SEVERE ASTHMA

It is important to be able to distinguish uncontrolled or difficult-to-control asthma when evaluating a patient with uncontrolled severe asthma due to suboptimal management from truly uncontrolled severe asthma.<sup>1</sup> The Global Initiative for Asthma (GINA) defines severe asthma as asthma that is uncontrolled despite adherence with an optimised high-dose combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) therapy, or that requires high-dose ICS-LABA to remain controlled.<sup>2</sup> Patients with severe asthma consistently face physical, mental, economic, and social burdens due to suboptimal management and care deficiencies.<sup>1,2</sup>

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CHAN KWOK WAI ADRIAN  
Respiratory Physician  
Mouth Elizabeth Novena Hospital Singapore

### CONFIRMING SEVERE ASTHMA DIAGNOSIS IN PRIMARY CARE

The first step towards adequate treatment of a patient with severe asthma is to establish a secure diagnosis and to address and eliminate factors that may aggravate or complicate the disease. Confirming the diagnosis is important as many conditions may mimic severe asthma and some patients may not have asthma at all.<sup>2,3</sup> Evaluation of severe uncontrolled asthma begins with an assessment of medication adherence and inhaler technique.<sup>1</sup> As many as 80 percent of patients with asthma are found to be poorly adherent to inhaled preventers,<sup>1,4</sup> stressing the importance of this first step.

If the history and physical examination suggest asthma as a likely diagnosis, GINA<sup>2</sup> recommends performing objective testing, such as spirometry before and after bronchodilator administration to evaluate baseline lung function and variability in airflow limitation. The presence of airflow obstruction is defined by a ratio of forced exhaled volume in the first second (FEV<sub>1</sub>) to the forced vital capacity (FVC) less than the lower limit of normal.<sup>5</sup> An increase in FEV<sub>1</sub> or FVC by greater than 12 percent and greater than 200 mL after bronchodilator administration indicates a positive bronchodilator response. If initial reversibility testing is negative (<200 millilitre or <12 percent increase in FEV<sub>1</sub>), a repeat of spirometry when symptomatic should be considered.<sup>2,5</sup>

Another method of assess variability when spirometry is normal or not available is to provide the patient with a peak flow diary. Bronchoprovocation testing for airway hyperresponsiveness in a tertiary centre can be considered if the patient can withhold bronchodilators (short-acting  $\beta$ -agonist (SABA) for at least 6 hours and LABA for up to two days depending on the duration of action of the controller).<sup>2,5</sup> Primary care physicians are recommended to seek specialist advice if the patient's history is suggestive of asthma, but the diagnosis cannot be confirmed by spirometry.<sup>2</sup>

For patients with frequent symptoms and/or exacerbations despite administration of high-dose ICS, the clinical or inflammatory phenotype should be assessed, as this may guide in tailoring therapy according to the phenotype. Some common phenotypes include early-onset allergic asthma, late-onset eosinophilic asthma, obesity-related asthma, exercise-induced asthma, and neutrophilic asthma.<sup>1,2,6</sup> The assessment of severe asthma phenotypes is performed by a specialist, preferably in a multidisciplinary severe asthma clinic where available.<sup>2</sup>

## OVERUSE OF OCS: WHEN IS IT TOO MUCH?

Frequent or continuous oral corticosteroids (OCS) often indicates that a patient may need an updated treatment plan or support with adherence to asthma medications.<sup>7</sup> Overuse of OCS is also associated with a significant risk of systemic side effects.<sup>8</sup> As many as 93 percent and 60 percent of patients with severe or difficult-to-treat asthma have received short- and long-term OCS treatment in the past 12 months, respectively.<sup>9</sup>

Hypertension, osteoporosis, cataract, diabetes, respiratory infections, and cardiovascular events represent some of the OCS-related major adverse events described in severe asthmatics.<sup>8</sup> A seven-year observational study conducted by Price *et al.*<sup>10</sup> in a broad asthma population (initiating OCS) reported that increasing cumulative exposure and mean daily exposure to OCS significantly places patients at a high risk of potentially life-changing OCS-related adverse outcomes. Cumulative annual OCS exposure as little as 0.5–1 gram (2–4 lifetime courses) was associated with serious adverse events (AE).<sup>10,11</sup>

These findings<sup>8–11</sup> further stress the importance of improving patient awareness on OCS-related adverse effects (AEs) and support the need for optimizing asthma treatments (ICS-LABA, long-acting muscarinic agonists (LAMA) and biologic therapies) to reduce exposure to OCS.

## IMPACT OF COVID-19 LOCKDOWN

The COVID-19 pandemic has brought about many challenges in terms of healthcare services/routines, diagnosis, management, and follow-up in common respiratory diseases, particularly asthma.<sup>12</sup> The shift from elective to essential or acute management in the healthcare setting has also limited the access to diagnostic resources for chronic respiratory patients, such as pulmonary function labs and sleep labs.<sup>12,13</sup> The restrictions and limitations placed on pulmonary function testing may further contribute to delayed diagnosis in non-severe patients with asthma.

Many countries, however, reported a reduction in asthma exacerbations, emergency healthcare visits, and influenza-related illness in the past year.<sup>2,14</sup> This observed trend may be due to the physical distancing and increased hygiene measures imposed worldwide. Additionally, an increase in the fear of acquiring COVID-19 measured among patients with asthma<sup>14,15</sup> might have led to a decrease or delay in healthcare visits. Innovative approaches using tools, such as teleconsultation and digital medicine services, are strongly encouraged to ensure sustained follow-up and good communication with patients especially when self-administration of treatment is done.<sup>14,16</sup>

Physicians should continue to manage asthma according to currently accepted asthma guidelines and recommendations. All prescribed medications, particularly ICS, should be continued, and OCS and biologics can be considered

wherever needed.<sup>2,17</sup> Guidelines have also recommended avoiding the use of nebulisers and spirometry, if possible, to reduce the risk of viral transmission.<sup>2,17</sup>

## ACCELERATING REFERRAL FROM PRIMARY TO TERTIARY CARE

Severe asthma may be under-recognised in primary care settings. Despite guidance provided by asthma management guidelines on when patients with asthma should be referred, failure and/or delay in referring patients to specialist consultation (tertiary care) is evident.<sup>18,19</sup> The primary care physician plays an important role in recognising severe asthma, exploring the need for escalation of therapy, and referring the appropriate patients for specialist assessment.<sup>20</sup>

A patient with asthma should be referred or reviewed at least once by an asthma specialist if he/she has received two or more courses of OCS in the preceding year, has poor symptom control despite good adherence and inhaler technique, or has been hospitalised for asthma care.<sup>20</sup>

The Global Initiative for Asthma (GINA) recommends considering referral to a specialist or severe asthma clinic if:<sup>2</sup>

- There is difficulty confirming the diagnosis of asthma.
- The patient has frequent urgent healthcare utilisation.
- The patient needs frequent or maintenance OCS.
- Occupational asthma is suspected.
- There is a food allergy or anaphylaxis, as this increases the risk of death.
- Symptoms are suggestive of infective or cardiac causes.
- Symptoms are suggestive of complications, such as bronchiectasis.
- There is the presence of multiple comorbidities.

To further expedite patient assessment and aid general physicians in the evaluation of patients with asthma who may benefit from referral to specialist care, AsthmaID was developed via a collaboration with asthma experts as part of the AstraZeneca-supported PRECISION programme.<sup>21</sup> The AsthmaID tool uses four straightforward questions (Figure 1) developed by five asthma experts based on GINA, to detect patients with asthma in need of a specialist referral.<sup>2,21,22</sup> General physicians in Singapore can access the web-based interface for AsthmaID ([www.asthmaID.sg](http://www.asthmaID.sg)) to answer the four questions and obtain additional information regarding asthma management via the AsthmaID portal.<sup>21,22</sup>

### ASTHMAID QUESTIONS

**Q1:** Has the patient used two or more courses of OCS over the past 12 months and/or is using maintenance OCS therapy?

**Q2:** Has the patient had two or more emergency attendances or unscheduled visits due to asthma over the past 12 months?

**Q3:** Has the patient ever been intubated or admitted to an ICU or a high dependency unit due to their asthma?

**Q4:** How many SABA inhalers has the patient used over the past 12 months?

**Figure 1. AsthmaID consists of four questions fit for use in most primary care settings without the need for additional testing or patient assessments. Patient referral to asthma specialist is recommended if 'Yes' is answered to questions 1, 2 or 3 and/or  $\geq 3$  SABAs is used by the patient in the past 12 months.**

OCS: Oral corticosteroid; ICU: Intensive care unit; SABA: Short-acting  $\beta$ -agonist.

Combining primary and tertiary care data in severe asthma registries would allow seamless monitoring of a patient's medical data through the healthcare system and improve communication between primary physicians and tertiary specialists. Singapore is currently part of the International Severe Asthma Registry (ISAR), a global collaborative initiative to gather anonymous, longitudinal, real-life data for patients with severe asthma worldwide.<sup>23</sup> This collaboration with ISAR provides a platform for physicians to understand and improve symptoms, treatments, and patient outcomes for severe asthma. This in turn can improve the standard of care for patients with severe asthma in Singapore.<sup>23</sup>

### CONCLUSION

Closing the care gap between severe asthma and difficult-to-treat asthma can only be achieved through a thorough evaluation and correction of factors contributing to poor asthma control before confirming the diagnosis. Furthermore, increasing patients' awareness as well as physicians' knowledge about asthma phenotypes and treatment options besides oral corticosteroids may be the key towards the improvement of overall asthma management in patients. Referral to tertiary care or an asthma specialist is indicated for patients with severe or difficult-to-control asthma, and a collaborative approach between primary care physicians and asthma specialists will improve long term severe asthma care.

### REFERENCES

- Côté A, Godbout K, Boulet LP. The management of severe asthma in 2020. *Biochem Pharmacol*. 2020 Sep;179:114112. doi: 10.1016/j.bcp.2020.114112. Epub 2020 Jun 27. PMID: 32598948.
- Global Initiative for Asthma (GINA). 2021 GINA Report, Global strategy for asthma management and prevention [Internet]. US: GINA; [updated 2021; cited 2021 June 26]. Available from: <https://ginasthma.org/gina-reports>
- Hashimoto S, Bel EH. Current treatment of severe asthma. *Clin Exp Allergy*. 2012 May;42(5):693-705. doi: 10.1111/j.1365-2222.2011.03936.x. Epub 2012 Jan 18. PMID: 22251278.
- Van Boven JFM, Koponen M, Lalic S, George J, Bell JS, Hew M, Ilomaki J. Trajectory Analyses of Adherence Patterns in a Real-Life Moderate to Severe Asthma Population. *J Allergy Clin Immunol Pract*. 2020 Jun;8(6):1961-1969.e6. doi: 10.1016/j.jaip.2019.12.002. Epub 2019 Dec 16. PMID: 31857262.
- Wu TD, Brigham EP, McCormack MC. Asthma in the Primary Care Setting. *Med Clin North Am*. 2019 May;103(3):435-452. doi: 10.1016/j.mcna.2018.12.004. PMID: 30955512; PMCID: PMC6776421.
- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012 May 4;18(5):716-25. doi: 10.1038/nm.2678. PMID: 22561835.
- Allergy & Asthma Network. Oral corticosteroid stewardship statement [Internet]. Austria: Allergy & Asthma Network; [updated 2018 November; cited 2021 June 26]. Available from: <https://allergyasthmanetwork.org/wp-content/uploads/2020/07/oral-corticosteroid-stewardship-statement.pdf>
- Caminati M, Vaia R, Furci F, Guarnieri G, Senna G. Uncontrolled Asthma: Unmet Needs in the Management of Patients. *J Asthma Allergy*. 2021 May 3;14:457-466. doi: 10.2147/JAA.S260604. PMID: 33976555; PMCID: PMC8104981.
- Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, Alacqua M, Tran TN. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *Am J Respir Crit Care Med*. 2020 Feb 1;201(3):276-293. doi: 10.1164/rccm.201904-0903SO. PMID: 31525297; PMCID: PMC6999108.
- Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, Tran TN. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018 Aug 29;11:193-204. doi: 10.2147/JAA.S176026. PMID: 30214247; PMCID: PMC6121746.
- Tran TN, King E, Sarkar R, Nan C, Rubino A, O'Leary C, Muzwidzwa R, Belton L, Quint JK. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *Eur Respir J*. 2020 Jun 4;55(6):1902363. doi: 10.1183/13993003.02363-2019. PMID: 32165402; PMCID: PMC7270349.
- Hughes-Visentin A, Paul ABM. Asthma and COVID-19: What do we know now. *Clin Med Insights Circ Respir Pulm Med*. 2020 Oct 23;14:1179548420966242. doi: 10.1177/1179548420966242. PMID: 33173369; PMCID: PMC7588760.
- Crimi C, Impellizzeri P, Campisi R, Nolasco S, Spanevello A, Crimi N. Practical considerations for spirometry during the COVID-19 outbreak: Literature review and insights. *Pulmonology*. 2020 Aug 5;S2531-0437(20)30175-6. doi: 10.1016/j.pulmoe.2020.07.011. Epub ahead of print. PMID: 32800783; PMCID: PMC7405879.
- De Boer G, Braunstaal GJ, Hendriks R, Tramper-Stranders G. Asthma exacerbation prevalence during the COVID-19 lockdown in a moderate-severe asthma cohort. *BMJ Open Respir Res*. 2021 May;8(1):e000758. doi: 10.1136/bmjresp-2020-000758. PMID: 33952584; PMCID: PMC8102860.
- Paggiaro P, Barbaglia S, Centanni S, Croce D, Desideri E, Giustini S, Micheletto C, Musarra A, Scichilone N, Trama U, Zedda MT, Canonica GW. Overcoming Barriers to the Effective Management of Severe Asthma in Italy. *J Asthma Allergy*. 2021 May 10;14:481-491. doi: 10.2147/JAA.S293380. PMID: 34007186; PMCID: PMC8121981.
- Benfante A, Scichilone N. Prioritizing care for severe asthma during SARS-CoV-2 pandemic. *Pulmonology*. 2021 May-Jun;27(3):189-190. doi: 10.1016/j.pulmoe.2020.08.001. Epub 2020 Aug 24. PMID: 33208299; PMCID: PMC7444931.
- Ong KY, Tan TL, Chan AKW, Tan KLL, Koh MS. Managing asthma in the COVID-19 pandemic and current recommendations from professional bodies: a review. *J Asthma*. 2020 Aug 11:1-8. doi: 10.1080/02770903.2020.1804578. Epub ahead of print. PMID: 32779943.
- Blakey JD, Gayle A, Slater MG, Jones GH, Baldwin M. Observational cohort study to investigate the unmet need and time waiting for referral for specialist opinion in adult asthma in England (UNTWIST asthma). *BMJ Open*. 2019 Nov 21;9(11):e031740.

- doi: 10.1136/bmjopen-2019-031740. PMID: 31753883; PMCID: PMC6887034.
19. Ryan D, Heatley H, Heaney LG, Jackson DJ, Pfeffer PE, Busby J, Menzies-Gow AN, Jones R, Tran TN, Al-Ahmad M, Backer V, Belhassen M, Bosnic-Anticevich S, Bourdin A, Bulathsinhala L, Carter V, Chaudhry I, Eleangovan N, FitzGerald JM, Gibson PG, Hosseini N, Kaplan A, Murray RB, Rhee CK, Van Ganse E, Price DB. Potential Severe Asthma Hidden in UK Primary Care. *J Allergy Clin Immunol Pract*. 2021 Apr;9(4):1612-1623.e9. doi: 10.1016/j.jaip.2020.11.053. Epub 2020 Dec 9. PMID: 33309935.
  20. Humbert M, Bourdin A, Papadopoulos NG, Holgate ST, Hanania NA, Halpin DMG, Chapman KR, Gavornikova M, Price DB, Kaplan A, Heaney LG. Reducing the hidden burden of severe asthma: recognition and referrals from primary practice. *J Asthma*. 2021 Jul;58(7):849-854. doi: 10.1080/02770903.2020.1759084. Epub 2020 May 13. PMID: 32347748.
  21. Bennett O, Mariko SK, Maarten B, Julie H, Tan TL. The AsthmaID Tool in Singapore: Four Simple Questions to Detect Patients in need of an Asthma Review by a Specialist. *The Singapore Family Physician*. 2021 Jan; 47(1): 50-53 doi: 10.33591/sfp.47.1.uo1.
  22. AstraZeneca. Asthma Referral Identifier [Internet]. SG: AstraZeneca; [updated 2021 March; cited 2021 June 27]. Available from: <https://www.asthmaid.sg/>
  23. ISAR. International Severe Asthma Registry [Internet]. UK: ISAR; [updated 2021; cited 2021 June 27] Available from: <https://isaregistries.org/>

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## LEARNING POINTS

- **Severe asthma as asthma that is uncontrolled despite adherence with an optimised high-dose combination of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) therapy, or that requires high-dose ICS-LABA to remain controlled.**
  - **A confident diagnosis of asthma can be made with a demonstration of reversible obstruction on spirometry.**
  - **Oral corticosteroid use is prevalent in asthma management, and the risks of adverse events and complications increase with the cumulative oral corticosteroid dosage.**
  - **Referral to tertiary care or an asthma specialist is indicated for patients with severe or difficult-to-control asthma.**
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