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UNIT NO. 2

THE ROLE OF AIRWAY INFLAMMATION IN ASTHMA

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ABSTRACT

Uncontrolled airway inflammation contributes to persistent asthma symptoms and risks of exacerbations and airway remodelling. Many asthma patients are non-adherent to inhaled corticosteroid (ICS) treatment and have a discordance between subjective symptom perception versus actual control of asthma, i.e. airway inflammation. Objective measurements of airway inflammation, e.g. FENO and sputum cell count quantification can aid clinical management. Nonetheless, there are many limitations in the tests' availability and interpretation. Hence, these tests are used mainly for difficult-to-treat or severe airway diseases. In the 2019 Global Initiative for Asthma (GINA) strategy report, short-acting beta-agonist (SABA) monotherapy is no longer recommended in Step 1 and ICS is recommended across all asthma severity to emphasize the importance of controlling airway inflammation. Doctors should discuss and recommend the most appropriate ICS therapy (dosing regimen and inhaler device) that is acceptable to the patient, to promote adherence. Appropriate use of ICS is crucial in achieving the management targets of asthma: maintenance symptom control and prevention of asthma risks.

Keywords:
Asthma; Airway inflammation; Sputum cell count quantification; F_ENO

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INTRODUCTION

Asthma is the commonest chronic respiratory disease globally, and with urbanization, its burden is expected to increase.[1] In Singapore, the prevalence is 5 percent in adult and as high as 20 percent in children. It is a heterogeneous disease characterized by three pathological components: airway inflammation, airflow obstructive and hyperresponsiveness.[2] Because uncontrolled airway inflammation leads to poor symptom control and future risks of exacerbations and airway remodelling, inhaled corticosteroids (ICS) is the mainstay of asthma treatment.

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WHEN AND HOW TO MEASURE AIRWAY INFLAMMATION

In the Asthma Insights and Management survey which interviewed 3000 asthmatics from different Asia-Pacific countries, approximately 50 percent have uncontrolled asthma and suffer from exacerbations.[3] This is attributed to the poor symptom perception and low ICS usage. Only 25-50 percent are on ICS therapy, and 40-60 percent rely solely on SABA monotherapy. In the patients who reported good asthma control, the majority have uncontrolled disease based on objective GINA symptom score criteria; this highlights the limitation of self-reported asthma control.

Tests for measuring airway inflammation,e.g. fraction of exhaled nitric oxide (FENO) and sputum cell count quantification (SCCQ) can objectively evaluate the presence of uncontrolled disease.[4, 5] However, they are not widely available nor routinely assessed. The pros and cons of both tests are summarised in Table 1. Hence, tests of airway inflammation is usually reserved for patients who have severe airway disease, e.g. severe asthma,[6] refractory cough, chronic obstructive pulmonary disease (COPD)/ bronchiectasis with recurrent infective exacerbations.[5] It can also be used in the assessment of difficult-to-treat asthma, defined as asthma that is contributed more by coexisting conditions (allergic rhinitis, gastroesophageal reflux etc), risk factors (smoking, inhaler technique issues, poor adherence) and triggers (environmental irritant/ aeroallergen exposure, pollution, menstruation, non-steroid anti-inflammatory drugs/ beta-blockers).[7]

THE ROLE OF BLOOD EOSINOPHIL COUNT IN SEVERE ASTHMA

In severe eosinophilic asthma,a relatively high blood eosinophil (typically defined as $\geq 0.3 \times 10^9$/L),[8] despite high dose ICS or systemic corticosteroids is a useful surrogate biomarker that can predict treatment response to anti-eosinophilic biologics that target the interleukin (IL)-5 (e.g. mepolizumab, benralizumab, reslizumab)and IL4/13 pathways (dupilumab). However, it has poor correlation with sputum eosinophil levels and has limited utility in monitoring and treatment titration.

Table 1: Difference in techniques and clinical applicability between F_ENO and sputum cell count quantification

	F_ENO*	Sputum cell count quantification
Logistic		
Availability	Typically done in tertiary healthcare settings	Usually only in selected severe asthma research centres
Technique	Takes 5 minutes, patients must be able to maintain steady expiratory flow. Measured using a single-breath chemiluminescence analyser, at an expiratory flow rate of 50 $mL \cdot s^{-1}$	Takes 60-90 minutes for sputum processing. Induced or spontaneous sputum sample is first collected. Sputum mucus is then lysed and filtered to form a cell suspension which is then made into cytospin slide to calculate the total and differential cell counts.
Risk	None	Related to sputum induction (bronchospasm)
Cut off levels	Different thresholds depending on study design and patient profile. • In mild-moderate, non-smoking steroid-naïve patients with asthma, ≥30 ppb** in children and ≥50 ppb in adults may signal the presence of eosinophilic inflammation and good treatment response to ICS. • In difficult-to-treat/ severe asthmatics. 'High' F_ENO might be associated with poor ICS adherence • See below for caveats in interpretation of test result	Differential cell count Eosinophil cut-offs • > 3 percent - high • ≥ 10 percent - severe Neutrophil • > 67 percent - high
Clinical utility		
Disease indications	Asthma	Severe airway disease (severe asthma, COPD/ bronchiectasis with recurrent exacerbations) and refractory cough
To confirm diagnosis of asthma	Not routinely recommended. It is not specific and can be elevated in non-asthma conditions, e.g. (allergic rhinitis, chronic rhinosinusitis, eosinophilic bronchitis, viral bronchitis, atopy, eczema). It can be also be low in asthma patients with neutrophilic asthma and if they are currently on ICS.	Yes, to confirm the presence, severity and type of airway inflammation. Its use is reserved mainly for endotyping severe asthma; it can differentiate between eosinophilic, neutrophilic or mixed airway inflammation.
To predict response to corticosteroid treatment	Possible, if F_ENO is high. A low F_ENO does not mean that it is safe to withhold ICS in a patient with asthma.	Yes
To titrate corticosteroid treatment	Not recommended routinely. Possible utility in children and pregnant women,[9-11] based on small studies.	Yes[12] SCCQ guided treatment can reduce exacerbations and improve control, in moderate to severe asthma.[12]
Summary	Not routinely recommended as it is difficult to interpret	It is recommended in selected difficult-to-treat and severe asthmatics, for endotyping,[13] treatment titration. This test is available only in specialised centres.

*F_ENO: fraction of exhaled nitric oxide, **ppb: parts per billion, SCCQ: sputum cell count quantification

CLINICAL RELEVANCE OF CONTROLLING AIRWAY INFLAMMATION

The addition of ICS even patients mild asthmatics with infrequent symptoms and exacerbations, could significantly reduce the risk of severe exacerbations and deaths.[14, 15] Though SABA monotherapy can provide temporary symptom relief, it can paradoxically worsen airway inflammation and asthma control.[16] Excessive SABA use (defined as one cannister every month) is strongly associated with asthma deaths.[17] Nonetheless, despite these evidence, long term adherence to daily ICS is poor and declines over time, especially in mild asthmatics.[18, 19]

The 2019 Global Initiative of Asthma (GINA) strategy report acknowledges that though ICS is crucial in asthma management, it is extremely challenging for doctors to convince mild asthmatics to initiate and adhere to daily low dose ICS. Hence after 30 years, GINA has made their most significant change in asthma management.[20] It no longer recommends short-acting beta-agonist (SABA) monotherapy and proposes a new option of asthma control using symptom-guided ICS treatment at Step 1. Many countries have yet to adopt this option officially. The key points are summarized (Table 2).

There are some important caveats. First, Step 1 treatment targets very mild asthma patients with symptoms less than twice a month with no risk factors for exacerbations. Many doctors find it difficult to distinguish between Step 1 and Step 2 might end up under-dosing ICS therapy. Second, the recommendation of "as-needed low dose ICS-formoterol (form)" in GINA Step 1 and Step 2 of asthma management is off-label[1]. Data currently exists only for budesonide (bud)-form.[19, 21, 22] There is indirect evidence to support the safety and efficacy of beclomethasone dipropionate (BDP)-form, but mainly from single maintenance and reliever therapy (MART) studies.[23] The efficacy and safety of fluticasone propionate (FP)-form for the two options (as-needed therapy and MART) is currently uncertain.

Table 2: GINA 2019: key changes for adults and adolescents above 12 years of age

Changes	Rationale
Step 1: SABA-only treatment is no longer recommended for safety reasons	The addition of ICS can reduce the risk of severe exacerbations and deaths even in mild asthmatics.[14, 15]
Step 1-2 options - Daily ICS - As needed ICS-formoterol (form) - As-needed low dose ICS whenever SABA is taken	In step 1, as-needed (symptom-driven) ICS treatment is recommended to allow self-titration of ICS dose according to changes in asthma control, especially since adherence to daily ICS is usually low at ~ 50 percent.[19] Recent studies in mild asthmatics (step 1-2) showed that compared to daily ICS, as-needed budesonide-formoterol is: [19, 21, 22] - Equivalent in preventing overall exacerbations - Superior at preventing severe asthma exacerbations requiring urgent visits (relative risk reduction 0.44)[19] - At a lower ICS maintenance dose (by approximately 25-50 percent).[19, 21]
Reliever of choice: - Step 1-2: As needed low dose ICS-formoterol is preferred to as-needed SABA - Step 3-5: either option.	In Step 1-2: as needed budesonide-formoterol is superior to SABA in preventing exacerbations.[19, 21] In Step 3-5: For patients on other maintenance ICS-LABA combination, as-needed SABA should be used as reliever. Low-dose ICS-formoterol is the preferred reliever for patients only when prescribed with MART regimen.
As-needed low dose ICS-formoterol should not be confused with the Maintenance and Reliever Therapy (MART)	MART is approved for moderate-to-severe asthma in Step 3 and Step 4. MART evidence is based on trials using budesonide-formoterol[24] and beclomethasone-formoterol[23]

Physicians would need to exercise their discretion when deciding to start low dose ICS versus as-needed low dose ICS-form (off-label recommendation) in Step 1 and Step 2. In Singapore, ICS-form options currently available include: (a) bud-form, (b) BDP-form and (c) FP-form. The estimated daily dose range and clinical comparability of "low dose" ICS (GINA 2019 (Box 3-6)): (a) budesonide (200-400mcg) (b) BDP extra-fine (100-200 mcg) (c) fluticasone propionate (100-250 mcg). Treatment decisions should take into consideration each patient's disease characteristics (control/ risk/ severity), personal preference and practical issues (inhaler technique, cost, etc.) to maximize adherence to ICS. We are awaiting more robust cost-effectiveness analysis and long-term safety data.

CONCLUSION

Many asthma patients are non-adherent to ICS treatment and have poor symptom perception despite having uncontrolled asthma. Objective measurements of airway inflammation, e.g. F_ENO and sputum cell count quantification can aid clinical management. Nonetheless, there are many limitations in the tests' availability and interpretation. Hence, these tests are indicated mainly for difficult-to-treat or severe airway diseases. In the 2019 GINA strategy report, SABA monotherapy is now "outlawed", and ICS is recommended across all asthma severity. Appropriate use of ICS is crucial in achieving the management targets of asthma - maintain symptom control and reduce asthma risks.

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LEARNING POINTS

- **Uncontrolled airway inflammation contributes to persistent asthma symptoms and risks of exacerbations and airway remodelling.**
- **Tests of airway inflammation can be used to objectively endotype airway disease and aid clinical management. However, there are issues with interpretation and availability of these tests. Hence it is used mainly in difficult-to-treat and/ or severe airway diseases.**
- **The key changes in the 2019 Global Initiative of Asthma (GINA) strategy report are (a) short-acting beta-agonist (SABA) monotherapy is no longer recommended in step 1 (b) ICS is recommended across all asthma severity.**