

# Management of bronchial asthma in 2021

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Dear Editor,

The Global Initiative for Asthma (GINA) 2021 update was published on the 28<sup>th</sup> of April, 2021 [1]. There are significant changes, including treatment of mild asthma, the role of azithromycin, treatment of asthma in COVID-19 times, and role of biologics.

## Treatment algorithm

GINA has updated the treatment algorithm for adults. The algorithm now highlights two options based on the choice of the reliever therapy. The first option is using a low dose inhaled corticosteroid-

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formoterol (ICS-F) combination as the reliever at all steps of management, with ICS-F being the maintenance therapy at steps 3-5. This preferred option [2] is derived from literature which has shown reduction in risk of severe exacerbations with ICS-F combination as a reliever therapy than a short-acting beta-agonist (SABA) alone despite a similar symptom control.

The other option uses SABA as a reliever therapy at all steps, with ICS taken with the reliever at step 1 and maintenance at step 2. The option is reserved for cases where the ICS-F reliever therapy is not possible or not preferred by a patient. Before prescribing, the physician should consider whether the patient is likely to be adherent with their controller therapy; else, this option might expose them to a higher risk of exacerbation with SABA-only therapy.

Thus, in simple terms, both options have different step 2 (daily ICS or as-needed ICS). The evidence stems from SYGMA1 [3], SYGMA2 [4], novel START [5] and PRACTICAL [6] trials, which found better symptom control with ICS-F combination than SABA monotherapy alone. Besides, SABA over-usage has been associated with increased exacerbations and mortality, as highlighted in a recent study (global SABINA program) [7], which included over 360,000 patients from the Swedish registries.

Under the classification of mild asthma, 'intermittent' and 'persistent asthma' has been removed as both entities are at risk of severe exacerbations. One of the aims of therapies includes reducing this risk, which necessitates ICS-containing treatment.

## Long-acting muscarinic antagonists (LAMAs)

Triple therapy combinations containing ICS, LABA, and LAMA were added to the recommendations at step 5 for adults over 18 years. The evidence shows that adding LAMA to medium or high dose ICS-LABA improves lung function and reduces exacerbations. Two recently published parallel-group, double-blind, randomized, phase 3 trials [8] (TRIMARAN and TRIGGER) enrolling over 2500 patients of severe asthma found a significant reduction in exacerbation and improvement in lung function (co-primary endpoints) on the addition of LAMA to ICS-LABA as a single extra-fine triple therapy inhaler. A similar study published in 2021 (CAPTAIN study) [9] in over 2400 patients of uncontrolled moderate or severe asthma reported improved lung function on adding LAMA to the existing ICS-LABA therapy. However, there was no significant reduction in moderate and/or severe exacerbations. In addition, in both these studies, the symptom control usually remained unaffected.

## Role of blood eosinophils levels

In patients with severe asthma, the blood eosinophils should be repeated for confirmation if found low. This update is based on the

evidence that nearly two-thirds (65%) of patients on medium or high dose ICS-LABA had a change in their eosinophil levels over one year; driving to a change in eligibility for biologics in a recent study of over 700 patients taken from a control group of SIROCCO and CALIMA trials [10]. Most patients had a shift in the eosinophil levels by week 24 with low baseline eosinophil levels, which might have made them ineligible for biologics if not serially measured. Another study (STELLAIR) [11] in 872 patients followed for 24 weeks found a favourable omalizumab response in reducing exacerbations and oral steroid use irrespective of eosinophil levels.

## Role of azithromycin

Add-on azithromycin for patients aged  $\geq 18$  years with severe asthma (Step 5) has been recommended based on findings from a new meta-analysis incorporating three studies (including the AMAZES trial) 604 patients [12]. The meta-analysis found benefits in reducing steroid use in the eosinophilic and reduced antibiotic use in the non-eosinophilic phenotypes. Since the most significant evidence in asthma is with azithromycin, the term macrolide is substituted. The duration of therapy should be at least six months and prescribed after specialist opinion, electrocardiogram, sputum for atypical mycobacteria, and adequate consideration for emergent drug resistance.

## Exercise-induced bronchoconstriction (EIB)

GINA 2021 advocates the use of ICS-formoterol before exercise in EIB. The evidence for this is that a small randomized controlled trial (RCT) [13] in sixty-six individuals with EIB found a more significant benefit of budesonide and formoterol on-demand and budesonide and terbutaline on-demand to terbutaline alone on demand. The difference in forced expiratory volume in the first second on spirometry was insignificant between the two budesonide groups (regular ICS vs. on-demand ICS). However, the total dose of budesonide received was significantly (2.5 times) lower in the formoterol group.

## Role of burst dose of budesonide-formoterol

In the *post-hoc* analysis of an RCT (SYGMA1) [14], a one-day use of budesonide-formoterol as reliever medication associated with lower 21-day exacerbations than either as-needed terbutaline or budesonide. Each inhalation contained 200 mcg budesonide and six mcg formoterol. In addition, the risk was lower with a higher number of inhalations, i.e., six vs four vs two. Interestingly, the minimum number of inhalations used in the trial was two, and hence the effect of a single inhalation in a single day could not be concluded. A possible reason for this association cited by the authors was the ability of individuals to titrate the dose of as-needed budesonide-formoterol according to their symptoms at the onset itself, in addition to using an effective anti-inflammatory supplemented by a potent and rapidly acting bronchodilator. However, it contrasts with results observed with as-needed SABA, where a higher number of inhalations required at symptom onset are associated with a higher risk of exacerbations.

## Single maintenance and reliever therapy (MART)

In a meta-analysis of sixteen RCTs [15], the use of MART correlated with a significantly lower risk of exacerbations compared with similar or larger dose inhaled budesonide as controller and SABA as reliever therapies. The all-cause mortality was rare in both groups and was similar. Therefore, GINA 2021 advocates using ICS-F in the form of MART as the preferred option over using ICS-LABA as maintenance therapy and as-needed SABA, in steps 3-5 of treatment. The evidence behind both options is strong (Category A). However, the protection from SABA that MART affords makes it the preferred choice in GINA 2021.

## COVID-19 and asthma

It has been re-emphasized for patients to continue taking their prescribed asthma medications, particularly ICS. For patients with severe asthma, biological therapy or oral corticosteroids, if prescribed, must also be continued. Even though one study observed severe asthma as a risk factor for COVID-19 mortality, a meta-analysis of 131 studies including 410,382 patients found asthma is not associated with higher COVID-19 severity or worse prognosis [16]. Patients with asthma reported having a lower risk of death compared with patients without asthma [17]. COVID-19 vaccination is recommended for asthma patients.

Thus, the GINA 2021 is a detailed evidence-based guideline with recent updates on asthma management in COVID-19 pandemic times, treatment choices in asthma, role of eosinophil levels, role of azithromycin, and inhaled triple drug therapy. An appropriate understanding of these updates and the evidence behind them can help improve asthma management worldwide.

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