BACKGROUND

Asthma is globally prevalent and globally relevant. Prevalence is not just high and persistently rising in developed countries; but is also high in REP countries, although for different reasons. For instance, changing patterns of air, occupational, and indoor pollution, unplanned urbanization, packed cohabitation, etc. are important factors for REP-specific settings.

Achieving optimal control is the central aim of therapy yet there are considerable proportions of patients who fail to respond optimally to treatment. Many factors related to patients (e.g., adherence, environmental and lack of optimal education), practitioners (lack of following guidelines, lack of educating patients, lack of proactive approach in management, suboptimal interpretation of severity and control, etc.), public agencies (inability to make available inexpensive, affordable and guideline-required medications), researchers (lack of more objective composite approach that can be equally applied in practice set-ups of developed and resource-poor (REP) countries, promoting one-size-fits-all approach etc.) are noted. This indicates that a collaborative composite approach is necessary involving all stakeholders for achieving optimal asthma control. Particularly practitioners need to partner with the patients in defining personalized therapy goals and empower them to negotiate their own care by self-monitoring and self-management. Practitioners should also think to go beyond their personal beliefs (preferences, choices) and be proactive in the asthma management (management of comorbidities, barriers, etc.). These factors in fact indicate that the control is not solely related to severity of the underlying disease but how it is managed.

DEFINITION

The control of asthma is said to be achieved if, aspects related to impairment and risk are reduced or optimally controlled. For instance, firstly asthma symptoms, exacerbations, unscheduled hospital visits and hospitalizations are optimally prevented and secondly normal (or near-normal) pulmonary function is maintained. This should be achieved with minimal burden from treatment side effects. The treatment decisions (nature, type and degree) should ideally be based on these parameters. Patients may have their own interpretation about asthma control and should be correlated to clinical parameters (Table 1). Uncontrolled asthma characterizes that the asthma does not respond optimally to maximum guideline-directed management (Table 2).

ABSTRACT

Asthma is globally relevant and globally prevalent. Uncontrolled asthma is a serious challenge wherein one-third patients currently may not obtain desired degree of asthma control. The objective of this paper is to review the significance of various factors (i.e. barriers) that may affect the control of asthma and putative solutions. Many factors related to patients (e.g. adherence, environmental and lack of optimal education), practitioners (lack of following guidelines, lack of educating patients, lack of proactive approach in management, suboptimal interpretation of severity and control, etc.), public agencies (inability to make available inexpensive, affordable and guideline-required medications), researchers (lack of more objective composite approach that can be equally applied in practice set-ups of developed and resource-poor (REP) countries, promoting one-size-fits-all approach etc.) are noted. This indicates that a collaborative composite approach is necessary involving all stakeholders for achieving optimal asthma control. Particularly practitioners need to partner with the patients in defining personalized therapy goals and empower them to negotiate their own care by self-monitoring and self-management. Practitioners should also think to go beyond their personal beliefs (preferences, choices) and be proactive in the asthma management (management of comorbidities, barriers, etc.). These factors in fact indicate that the control is not solely related to severity of the underlying disease but how it is managed. Hence, it is likely that solving these barriers can help good proportion of those who are currently suboptimally controlled. Evaluation of asthma control in practice set-ups needs to be objectively and comprehensively defined.

TABLE 1 | Perspectives of asthma control

<table>
<thead>
<tr>
<th>No exacerbations</th>
<th>No need for steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroids ≤ 1 time/year</td>
<td>No fear of getting a cold or forgetting inhaler</td>
</tr>
<tr>
<td>No exercise limitations</td>
<td>I can exercise</td>
</tr>
<tr>
<td>No nocturnal awakening</td>
<td>I can sleep through the night</td>
</tr>
<tr>
<td>No school/work absences</td>
<td>I can go to school/work every day</td>
</tr>
<tr>
<td>No unscheduled hospital visits or hospitalization</td>
<td>Can meet friends</td>
</tr>
<tr>
<td>No uncontrolled upper airway symptoms</td>
<td>No problem with sinus</td>
</tr>
</tbody>
</table>
inhaler. Anecdotal reports indicate improvement or sometimes muscle mass or strength. Also, dyspnea in part results from inappropriate respiratory muscle efforts in these cases. It is seen that inspiratory muscles of those with COPD and asthma after training led to respiratory muscle efforts in these cases. 

Patients with asthma experience increased airway resistance and hyperinflation which puts respiratory muscles at a mechanical disadvantage. As with chronic obstructive pulmonary disease (COPD), those with asthma also show decreased respiratory muscle mass or strength. Also, dyspnea in part results from inappropriate respiratory muscle efforts in these cases. It is seen that inspiratory muscles of those with COPD and asthma after training led to decrease of dyspnea and use of beta-2 agonists. On the other hand, anecdotal reports indicate improvement or sometimes alleviation of asthma symptoms with yoga-derived exercises. Few randomized trials have addressed this although only one study has shown improvement in peak expiratory flow (PEF) while other studies have shown reduction in asthma exacerbations and the use of rescue beta-2 agonists. Improvement in quality of life (QOL) and a trend towards improvement of symptom score is also reported. Thus, exercises may have some relevance in asthma management especially since it allows patients to take charge of management (self-management) of their asthma to some extent.

**Difficult Devices**

Inhalation is the mainstay of treatment since it facilitates high bronchial concentration of drug without high systemic bioavailability but with reduced side effects. Optimal use of device is extremely crucial for optimal drug delivery, compliance, treatment efficacy and resultanty optimal control. Pressurized metered-dose inhalers are most commonly used inhalation device. Many studies report their inappropriate use in 14-90% of cases. This reduces drug delivery by 13% and 30% reduction in 1-second forced expiratory volume (FEV). These results indicate that suboptimal use leads to asthma instability from reduced availability and clinical efficacy of drug which in turn ends up into impaired asthma control. Inappropriate use is more important for old-age patients due to higher chances of coordination error. Other factors such as suboptimal knowledge and teaching about inhalation technique are also pertinent. Suboptimal use of other devices such as dry powder inhalers is reported to be less than metered-dose and is also low cost, equally efficacious, easier to handle and have lesser side-effects from its use such as discomfort, vocal performance, shimmer score, etc. Patient-partnership is of paramount importance in choosing the right device. One may choose the best possible device, but if it is not liked by the patient, it might be difficult to achieve an optimal use of that device and thus optimal asthma control in the same manner.

**Gastroesophageal Reflux Disease**

The epidemiological association between asthma and gastroesophageal reflux disease (GERD) has long been explored and the relation is two-way where one worsens another. A higher prevalence of GERD among asthma population is noted although that varies widely (up to 82% of those with asthma). GERD is one of the exacerbating factors for those with poorly controlled asthma. Mechanistically also the acid may get into the airways and cause increased airway reactivity, bronchoconstriction or chronic airway inflammation. Esophagitis and persistent cough also ensue with chronic acid reflux. Individual clinical trials show treatment of GERD improves asthma control whereas a large review of all such trials

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**TABLE 2 | Features defining uncontrolled asthma**

<table>
<thead>
<tr>
<th>Daily daytime symptoms</th>
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</thead>
<tbody>
<tr>
<td>Limitation in performing day-to-day activities</td>
</tr>
<tr>
<td>Weekly nocturnal symptoms and awakening</td>
</tr>
<tr>
<td>More need for rescue medications</td>
</tr>
<tr>
<td>Lung function (FEV1) &lt; 80%</td>
</tr>
<tr>
<td>Three or more exacerbations per year</td>
</tr>
</tbody>
</table>

Asthma is a dynamic disorder with on-and-off exacerbations and high variability, thus maintaining optimal adherence is important. This is more so in children who need support from their peers. Not maintaining this increases the risk for morbidity, mortality and treatment cost. Despite this the adherence is suboptimally achieved for minority of asthma cases, for example, from less than 30 to 70%. Less than 50% of children remain adherent to prescribed medications. Underwhelming situation is observed in this regard in five large states of India. Those who are nonadherent are at an increased risk for asthma instability and long-term poor outcome including unscheduled hospital visits, hospitalization, use of rescue steroids, etc. Delay in treatment onset is also an important factor for persistent symptoms, deterioration of lung functions, reduced treatment response and frequent exacerbations. Simplification of regimens, better patient education and communication, use of telecommunication techniques, lack of physician knowledge, lack of following treatment guidelines by practitioners, etc. are important for improved adherence and are given in Table 2.

Breathing Exercise

Patients with asthma experience increased airway resistance and hyperinflation which puts respiratory muscles at a mechanical disadvantage. As with chronic obstructive pulmonary disease (COPD), those with asthma also show decreased respiratory muscle mass or strength. Also, dyspnea in part results from inappropriate respiratory muscle efforts in these cases. It is seen that inspiratory muscles of those with COPD and asthma after training led to decrease of dyspnea and use of beta-2 agonists. On the other hand, anecdotal reports indicate improvement or sometimes alleviation of asthma symptoms with yoga-derived exercises. Few randomized trials have addressed this although only one study has shown improvement in peak expiratory flow (PEF) while other studies have shown reduction in asthma exacerbations and the use of rescue beta-2 agonists. Improvement in quality of life (QOL) and a trend towards improvement of symptom score is also reported. Thus, exercises may have some relevance in asthma management especially since it allows patients to take charge of management (self-management) of their asthma to some extent.

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Environmental

Exposure to environmental irritants not only increases the risk for development of asthma but also increase its morbidity for instance severity, exacerbations, unscheduled hospital visits and hospitalization. For these cases positive parental perceptions might play an important role in achieving an optimal asthma control. Pollutants produce strong inflammatory responses that in turn worsen the asthma symptoms, lung function, respiratory distress, increased medication use that all end up into asthma instability. These factors may also pose risk by inducing genetic variation in oxidative stress pathway. Living in traffic dense surroundings, near construction sites, having unclean ducts in air-conditioners, house dust mites may play a role in poor control and worsening of asthma. In desert-prominent populations, aeroallergens can also worsen asthma, cause unscheduled hospital visits and hospitalization. This is also true for those working in construction sites, sudden heavy exposure to dust, and sand-storms among uncontrolled asthma patients.

Gastroesophageal Reflux Disease

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Pulmonology

shows underwhelming results for both adults and children. These differences are most likely due to the biases from sample size or the incoherent parameters used in individual trials. Larger trials have shown mild improvement in PEF especially for those taking long-acting beta-2 agonists. Many factors such as localization of GERD, non-acid reflux such as bile, and neurogenically mediated airway inflammation are yet to be evaluated comprehensively. GERD may manifest poor lung function and respiratory symptoms through its intricate relation with obstructive sleep apnea (OSA) as well. Persistent cough and OSA occurring through GERD is well known.

Guidelines

Lack of following treatment guidelines by practitioners is not uncommon. Multitude of reasons may partially explain this practice for instance degree of specialization, lack of awareness of existing or updated guidelines especially of non-specialists, priority by individual practitioners to their own personal preferences, location of patient or practice, underestimated severity and severity misclassification of asthma etc. Health-system differences may partially have a role for instance infrequent discussion of asthma management among colleagues for instance. Taboo with the use of steroids is another major hindrance in optimal control. Guidelines recommend steroids as gold-standard yet they are insufficiently prescribed; preference for use of beta agonists as monotherapy although not useful; or preference for combination therapies at the start of the therapy, etc. are another hindrances.

Obstructive Sleep Apnea

Obstructive sleep apnea has some role to play in poorly controlled asthma and causes frequent exacerbations. Continuous positive airway pressure (CPAP) therapy for OSA in patients with nocturnal asthma improves asthma symptoms, rescue bronchodilator use, PEF, and QOL and stoppage of treatment cancels these benefits. Other studies in contrast show development or worsening of bronchial hyper-reactivity with CPAP. Putative benefits for those having daytime asthma are yet to be evaluated. OSA promotes other asthma triggers such as GERD. Obesity and OSA are other factors that independently lead to increased airways inflammation thus may facilitate poor asthma control in this scenario. Contrasting results in terms of airway obstruction and inflammation are however observed. Role of other factors such as local and systemic mechanisms for bronchial wall thickness, cough suppression, impaired symptom perception, etc. could have some role in pathogenesis. Those with asthma and OSA have lower levels of eosinophilic inflammation and noneosinophilic phenotype is especially noted with poorly controlled asthma.

Psychiatric

Factors such as anxiety and depression are reported to be modulators of poorly controlled asthma. These are frequently observed especially among those with untreated asthma. It is however uncertain whether these factors are consequence of poorly controlled asthma or the cause of it. This is partially because both asthma and anxiety are contrasting situations wherein anxiety has exaggerated perception of symptoms and in asthma patients may undermine their own symptomatic perception. This is partial explanation that these parameters might not always reflect in the objective measurements of asthma control such as asthma symptoms or QOL. To add, stress can cause pro-inflammatory states as seen with increased cytokine production. There might also be hormonal significance since anxiety and insomnia are more common among women with asthma. Irrespective of these contrasting observations, it is crucial to integrate these psychopathological states (fear, mood disturbance, anxiety, depression, etc.) when assessing asthma control and QOL. This is an important step since these negative psychopathological states may negatively affect treatment adherence and the chances of following the self-management plan diligently. These factors are crucial for achieving optimal asthma control.

Rhinitis

Both asthma and rhinitis are similar systemic airway inflammatory processes. Epidemiologically up to 38% of rhinitis patients have asthma while prevalence of rhinitis among those with asthma can be beyond 50%. Both allergic and nonallergic rhinitis have been associated with increased prevalence of asthma. For instance, those with allergic rhinitis there is a higher prevalence of asthma, food sensitivity, eosinophilia, increased total IgE, bronchial hyper-responsiveness while those with nonallergic rhinitis show higher prevalence of asthma alone. This suggests different endotypes of asthma with allergic and nonallergic rhinitis. Rhinitis often precedes asthma and can therefore present as a risk factor for asthma. Among children, however, asthma often precedes rhinitis. Studies indicate that optimal treatment of rhinitis reduces odds ratio for uncontrolled asthma as well as reduction in unscheduled hospital visits, missed work days, nocturnal awakening by about 50%. Similar results are obtained in asthma children among whom rhinitis is an important disorder. Asthma in rhinitis patients often triggers worse nasal symptoms and an improved control of these nasal symptoms frequently results in improved asthma symptom scores. Thus, the influence of untreated rhinitis is rather detrimental on asthma control. Despite this it is still not part of recommendations.

Self-Management

Continuous monitoring is essential to achieve treatment goals or to tailor the asthma therapy. Currently, many asthma cases fail to attend checkups or visit their physicians regularly thus paving way for the self-management. Self-management, excepting exacerbations, improves asthma control, lung function and the QOL among uncontrolled subjects. Similar overwhelming results are noted in a very large review of several clinical trials that showed that self-management reduced hospitalization, unscheduled hospital visits, days-off, nocturnal asthma, asthma symptoms, need for rescue medications and improvements of lung function, PEF and QOL. Self-management approach can also be particularly useful for achieving asthma control in subjects, for instances living in remote or rural residence.

Vaccination

Although 60–80% asthma cases have upper respiratory infections, particularly influenza, in the background but only few of them get vaccinated against influenza. Many times an increased risk of asthma exacerbations after influenza vaccination has been suspected but large reviews have not shown any link between two. On the other hand, a study did not find any reduction in asthma severity or fatal complications following influenza vaccination. Thus, in current scenarios vaccination remains the best strategy to reduce additional disease burden among asthma subjects.

Limited Access and Cost

There is a direct relation between severity and control of asthma with the availability and affordability of its treatment. Those who may access can increase their income and reduce their asthma-related expenditure (unscheduled visits, hospitalization, etc.) by about 40%. Currently, this is not the case though.

BRITTLE FORM OF ASTHMA

Being one of the variant of severe refractory asthma, this occurs in approximately 10% of severe asthma cases and 0.5% of all asthma
cases.\textsuperscript{70} It has two clinical subtypes (Table 3). These cases are phenotypically different and have particularly high risk of morbidities (hospital admission, treatment side effects, and psychosocial effects) and mortality (acute asthma, disease severity).\textsuperscript{76,77} These factors are sufficient to worsen the asthma control or precipitate exacerbations.

**THERAPEUTIC APPROACHES**

Conventional approaches are based on relievers (bronchodilators) and controllers (immunomodulators and/or anti-inflammatory agents). Relievers open airways and provide more symptomatic short-term relief while controllers are suitable for long-term relief by reducing hyper-reactivity and inflammation. Avoidance of exposure to relevant triggers is often the additional gold-step in the asthma management. Current therapies pragmatically propose one-size-fits-all approach consisting of bronchodilators and immunomodulator and/or anti-inflammatory agents. These can effectively control asthma but substantial number of cases fails to optimally respond. This is partially because practitioners/patients have been seen the tendency to underestimate their severity but overestimate the control of their asthma.

Several approaches are now available at different stages of their development that are based on: reducing airway smooth muscle, reducing airway inflammatory cell number or activity, optimization of bronchodilation, etc.

**Optimization of Bronchodilation**

Inhaled beta-2 agonists are likely to partially become less effective from their chronic use\textsuperscript{22} although optimal degree of bronchodilation is still likely to be maintained.\textsuperscript{73} Instead of its use with inhaled corticosteroids (ICS), studies have tested its use with long-acting muscarinic antagonists (tiotropium) and double dosed ICS in severe refractory asthma. The results showed better lung functions and asthma control with tiotropium when individually compared to double dosed corticosteroid or beta-2 agonists.\textsuperscript{73} This treatment in severe refractory asthma showed that addition of tiotropium, to inhaled corticosteroid and beta-2 agonists, significantly improved lung function.\textsuperscript{74}

**Add-on Options**

Inhaled corticosteroids are the mainstay of treatment for persistent asthma. Although significantly effective, at its usual doses, for number of cases, sizeable number of cases remains symptomatic with its use. Such patients are needed to be treated by: increasing ICS dose; or adding long-acting beta-agonist (LABA) or leukotriene-receptor antagonist (LTRA) or theophylline.\textsuperscript{73} Studies have shown that increasing the ICS dose does not provide sufficient improvement of most lung function and symptom parameters. A fourfold increase in dose however is noted to render improvements in the need of rescue beta-agonists, PEF, or the lung function, etc.\textsuperscript{76} Its anti-inflammatory activity does not improve with increasing the dose (4-16 folds).\textsuperscript{76,78} This suggests that current doses are likely to be sufficient for suppressing any inflammation in most patients. There is no conclusive evidence\textsuperscript{79,80} on the risk of systemic adverse effects with increasing the ICS dose, due to the heterogeneity of studies.

Some degree of dose-dependency in the HPA-axis effects of inhaled steroids is noted. A large meta-analysis showed increased risk for posterior subcapsular cataracts, and to a much lesser degree, the risk for ocular hypertension and glaucoma, and skin bruising, with high-dose exposure.\textsuperscript{80} Long-acting beta-agonist (long-lasting relaxation of airway smooth muscle) and ICS (potent anti-inflammatory effects) have complementary effects. ICS can also increase the expression of beta-2 receptors in inflammatory cells to overcome the desensitization in response to chronic beta-2 agonist exposure.\textsuperscript{81} In addition, LABA may prime the glucocorticoid receptor facilitating activation by corticosteroids.\textsuperscript{82} Proinflammatory effects with beta agonists are generally suspected although available studies are not seen to increase the inflammatory indices. This matches with other studies that indicate that there is no increase in number and severity of asthma exacerbation with their long-term use.\textsuperscript{82} Safety of this add-on therapy is not unpredictable and only results in slight increase in tremor and tachycardia; without any discontinuation of this therapy.\textsuperscript{83,85} This add-on has been found to be better than increasing the ICS dose by fourfold in reducing day/night time symptom score, asthma exacerbations, rescue therapy, etc.\textsuperscript{76,83,86} Cysteinyl leukotriene receptor-antagonists (LTRA) are a new class of asthma medication and have a weak anti-inflammatory activity. Since corticosteroids are not very effective inhibitors of cysteinyl leukotriene pathways\textsuperscript{87} and thus their combination may offer some benefit. Studies does not show different results that this, and many adult and children studies state that their combination reduce the number of patients who may need a systemic corticosteroid, compared to ICS alone [RR = 0.34; 95% CI 0.13, 0.88].\textsuperscript{88} This risk of
reduced exacerbations that may eventually need systemic steroids indicate that this may modestly improve asthma control compared with ICS alone but this strategy cannot be recommended as a substitute for increasing the dose of ICS.99 Other study however showed that addition of LTRA may be equal to doubling the dose of ICS,100 however, this was stated without including a placebo arm. More data is needed before this combination can be included as a more global practice. Theophyllines have bronchodilator effect, immunomodulatory, anti-inflammatory, and bronchoprotective effects.91 Studies indicate that there is an improvement in pulmonary function and asthma symptoms when theophyllines are added to ICS,92 although all studies have not been able to confirm this result.93 This combination may or may not equate to doubling the dose of ICS in the treatment of uncontrolled asthma. Side effects can be reduced by using a concentration slightly below the recommended range.

Inhaler Devices
Different devices are reported to have different difficulties, advantages and limitations. To what extent these differences affect clinical outcome in asthma subjects is inconclusive. A large review of different devices reported no significant difference in drug delivery and clinical effectiveness.94 In contrast, other studies report that certain devices (e.g. metered dose) are more difficult than rest95 and considerably affect compliance to treatment and asthma control. Another study reinstates the importance of choosing right inhaler for optimal asthma control.96 Patient training is another area that may improve compliance and asthma control. Many studies have highlighted importance of patient training and regular checking of patients’ inhalation techniques.97 Guidelines reinforce that an inhaler should only be prescribed after confirming that the patient knows how to use the device.98 Switching to cheaper alternatives, such as metered-dose, has been seen to worsen asthma control with greater need for emergency beta-agonists.99 This is more so if it is done without clinical consultation or training. All this should in fact be personalized, and guided by patient’s sociodemographic characters such as young or old age, trembling of limbs, affordability, literacy level, etc.

Asthma Control through Management of Comorbid Diseases
Effect of GERD on asthma is still debatable since improvement in asthma following GERD treatment is variable. Studies however show improvement of asthma symptoms for 69% cases following successful treatment for GERD.100 In another study, 24-week treatment with lansoprazole reduced asthma exacerbations and improved QOL, especially for those on polytherapy already.101 A recent large review confirmed this by stating significant association between GERD and asthma.102 Similar paucity of data is noted for OSA and results are currently more inconclusive than GERD. Mechanical changes from treatment with CPAP could influence airway responsiveness but other study did not find any such association. Treatment of psychopathologies such as panic attack, improves asthma outcomes although a large meta-analyses does not support this. In any case, more extreme psychopathologies such as bipolar disorder, etc. do not occur more frequently among those with asthma.103 The effect of intervention for obesity is much clear for improvement in asthma. A large review of 15 studies noted that each of the study that examined the effect of weight loss on asthma outcomes noted an improvement in at least one of the asthma related outcome.104 This effect stands irrespective of type of intervention, age, gender and ethnicity. Thus weight loss for improvement of asthma control should be stressed. Similarly cessation of smoking has similar effect on improving asthma outcomes. Although still debatable, there are number of reports that report an improvement of asthma following optimal management of allergic rhinitis. For instance, combined treatment with montelukast and budesonide had significant effect on reducing airflow obstruction. Other studies also indicate towards improvement in asthma control and QOL following successful treatment for allergic rhinitis.

Omalizumab
It is a recombinant DNA-derived humanized immunoglobulin G 1k monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and inhibits interaction of IgE with IgE receptors preventing the release of inflammatory mediators that occur in allergic asthma. This has therefore seen to cause significant, rapid and sustained reduction in serum free IgE levels at differing dosing regimens and in a dose-dependent fashion.105 This has also been seen to reduce airway eosinophilia in the mild asthma patients. Better clinical benefits are seen in many trials among those with moderate-severe asthma in terms of number of exacerbations and reduction of use of inhaled corticosteroids when compared with control.106,107 Among those with severe asthma Omalizumab led to longer steroid reduction phase and reduction in median corticosteroid dosage. This also decreases use of rescue medication, improves asthma symptoms as well as QOL.107 Among those with inadequately controlled severe persistent asthma despite best available therapy108 Omalizumab has shown improvements in severe exacerbation rate, unscheduled emergency visit rate, QOL, asthma symptom score, etc. For instance, reductions in hospitalizations due to asthma can be 92% lower,109 total emergency visit rate by 47% lower, and exacerbations by 38% lower versus placebo in patients with omalizumab-treated severe persistent asthma.110 Meta analysis also indicated a 1.6- to 2-fold increase in moderate (≥ 1 point) (P < 0.001) and 1.8- to 2.1-fold increase in large (≥ 1.5 point) [P < 0.001] improvements in overall QOL scores in Omalizumab-treated patients compared with placebo during both steroid stabilization and steroid reduction periods.111 Omalizumab has been extensively evaluated for adverse events and similar safety profile to that of the control group, with no significant differences between groups112 have been found among patients with moderate-to-severe persistent asthma. Similar safety profile is noted among children as well.

Reducing Airway Inflammatory Cell Number/Activity
Studies show that monitoring sputum eosinophil count might help in reducing the risk for severe exacerbations in the future.113 However, this seems to be useful for those with moderate-severe asthma only. Further studies have tested mepolizumab114,115 and reslizumab116 (anti-interleukin-5 monoclonal antibody) among hypereosinophilic patients having had severe refractory asthma. These treatments have shown clinical benefits in terms of corticosteroid sparing, number of future exacerbations, improved expiratory flow and overall asthma control. These effects are however not observed among those with less severe asthma117 indicating importance of patient-selection. For those who have mild allergic asthma, use of antihistase approach for reducing the level of messenger RNA and its translation into protein has been found to be effective in reducing airway eosinophils by inhibiting the production of cytokine receptors.118 Many subjects exhibit neutrophilic asthma instead and these subjects with neutrophilic severe refractory asthma have been demonstrated to benefit with chemokine receptor antagonists.119 Novel therapeutics120 such as with cytokine inhibitors, including daclizumab, etanercept, etc. have been tested in relation to refractory asthma. These compounds have been shown to improve asthma control; inhibit, in vitro, expression of inflammatory mediators such as interleukins 4, 5, and 13; decline in bronchial hyperresponsiveness, improvements in QOL and postbronchodilator FEV1. Similarly
lumixilimab, an anti CD23 antibody is shown to reduce IgE concentration by 40% and reduced production of proinflammatory cytokines, in patients with asthma.

Reducing Airway Smooth Muscle
Bronchial thermoplasty is a nonpharmacologic option that involves the delivery of radiofrequency to large airways in order to reduce the volume of smooth muscle and their responsiveness. Among patients with relatively better controlled asthma, reduction in mild-severe exacerbations and further improvement in asthma control has been noted with thermoplasty. Among those with severe refractory asthma, over a short follow-up period, thermoplasty has been found to reduce exacerbations and emergency hospital visits, improved morning peak expiratory flow and QOL (e.g. days lost due to asthma). Similar results are observed over a longer follow-up period of time such as absent complications and maintenance of stable lung function. Side effects among those with mild-moderate asthma are mild and self-limiting and include cough, dyspnea, wheezing, and bronchospasm. However those with severe asthma, the side effects are reported to be more frequent but these gradually balance out over time.

Patient’s selection for this therapy is therefore important.

FINAL REMARKS AND CONCLUSION
Currently the control of asthma is the recognized central theme in the asthma management while asthma severity paradoxically has taken the back-seat for now. Control is less likely to be independent of the disease severity because severity is closely related to the treatment response (i.e. degree of control). Thus, at first it might be necessary to integrate both parameters in the future management recommendations. No doubt, management of asthma needs to be improved. Much of the poor control of asthma can be attributed to the factors that are related to both practitioner (following treatment guidelines as recommended etc.) and patients (optimal adherence etc.). Thus, a comprehensive approach should be adopted where both practitioner and patient become partner together and support each other to achieve personalized predefined therapy goals. The level of asthma control likely to be achieved in patients reflects behavior of both patients and their practitioners. Practitioners must identify barriers at the start of therapy that likely hinder optimal control including residence in traffic or construction sites, adherence issues, ease in availability of medications, self-monitoring by the patients, optimal education of the patient, management of comorbidities (e.g. obesity, upper respiratory infections), etc. They should also aim to identify those are at risk of failing to achieve these or those who may have more severe forms such as brittle asthma. Thus a more composite yet personalized approach (Table 4 and Figure 1) should replace the current one size fits all approach. On the other hand, practitioners should align their personal beliefs (preferences or choices) with recommended guidelines and should be more effectively educated on the complexities of measuring asthma severity and initiate appropriate asthma treatment. These aspects would make sure that asthma is properly treated, monitored and managed and may result in desired degree of asthma control. Public agencies especially of REP countries should ensure that the diagnostic gap and treatment gap is reduced and suitable medications are easily available in an affordable manner. This would help patients not to self-prescribe or take suboptimal medications but help them to take regular controller medications and avoid taking treatment only at the time of complication or hospitalization. Researchers should adopt a collaborative approach for conducting organized research on uncontrolled asthma. This might facilitate faster advancement of our understanding about uncontrolled asthma.

**TABLE 4** Measures for difficult-to-control asthma

<table>
<thead>
<tr>
<th>Measures for difficult-to-control asthma</th>
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<tbody>
<tr>
<td>• Educate patient about treatment plan-rationale-goals</td>
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<tr>
<td>• Emphasize written asthma management plan and adherence to it</td>
</tr>
<tr>
<td>• Evaluate understanding about asthma and its medications</td>
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<tr>
<td>• Identify patients’ priorities in treatment</td>
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<tr>
<td>• Ask patients to demonstrate the use of technique for instance inhaler</td>
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<tr>
<td>• Ensure regular follow-up and evaluate measures of response</td>
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<tr>
<td>• Assess patient’s desire and commitment to treatment</td>
</tr>
<tr>
<td>• Follow treatment guidelines yourself</td>
</tr>
<tr>
<td>• Identify barriers to treatment (cost, availability, triggers, etc.)</td>
</tr>
<tr>
<td>• Identify and treat comorbidities</td>
</tr>
<tr>
<td>• Be proactive in alternative medication choices that are likely to meet patient goals</td>
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</tbody>
</table>
Learning more about the complexities of asthma pathophysiology will strengthen our therapeutic armaments for patients who do not respond well to conventional medications. Some of these have already shown promise for those with poorly controlled asthma for instance omalizumab, muscarinic antagonists, etc. The researchers should also define how newer treatments are going to be integrated into existing therapies.

To conclude, there are numerous barriers to meeting needs in asthma control and only a few have been explored here. Nevertheless, it is evident that a composite approach to asthma control by involving all stakeholders (patient, practitioner, researchers and public agencies) is necessary. These factors in fact also indicate that the asthma control is not solely related to severity of the asthma but how it is managed by the practitioners, patients and public agencies. Hence, solving some of these barriers can putatively help good proportion of those who are currently suboptimal controlled. Particularly practitioners need to partner with the patients in defining personalized therapy goals and empower them to negotiate their own care by self-monitoring and self-management. Practitioners should also think to go beyond their personal beliefs (preferences, choices) and be proactive in the asthma management (management of comorbidities, barriers, etc.). Evaluation of asthma control in practice set-ups needs to objectively and comprehensively defined. Needless to mention that better tools for assessment and monitoring of asthma are needed.


