Guideline Based Management of Bronchial Asthma

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“The need to know is compelling—it drives discoveries that can change the face of our world. Yet knowledge is redundant unless you can share it with others.”

Oxford University Press.

Guidelines have been around for the past 25 years and have clearly and positively impacted the level of care of asthmatics around the world. The first guidelines probably came out of New Zealand and Australia and these have been followed by a plethora of guidelines from various societies around the world; the most significant of which has been the GINA guidelines and the British Thoracic Society have also put forth a very elaborate and extensive guideline based approach. A study of the above two guidelines will give us a clear and precise understanding of the nuances of Asthma Therapy. These have probably been the most comprehensive and thorough evidence based approach towards practical treatment of asthma. They have formed a road map for the diagnosis, treatment and follow up patients with asthma.

While we shall go into the merits and demerits of the important guidelines specifically, one clearly understands the necessity to tailor make these guidelines to suit our ground realities in clinical practice. It is obvious that before we consider treatment options the question of making a definite diagnosis of asthma based on evidence — reversibility by spirometry is an absolute must. Mention should also be made of the quality of the spirometric recording to confirm to ATS/ERS specifications. The general starting point for a diagnosis of asthma must be a combination of clinical features plus an acceptable pulmonary function test.

There are multiple guidelines available with a clear level of uniformity in approach and content between them. We shall site here the BTS and GINA which are probably the most commonly
referred to guidelines by clinicians. One also needs
to understand the absolute necessity to marginally
modify guidelines to suit local conditions that exist
in every day practice. This is more obvious in a
country like India with its numerous cultural and
ethnic diversity.

**BTS**

<table>
<thead>
<tr>
<th>Inhaled B2</th>
<th>ICS</th>
<th>ICS/LABA</th>
<th>ICS/LABA</th>
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<tbody>
<tr>
<td>As required</td>
<td>400 mcg</td>
<td>ICS to 800 mcg</td>
<td>+LTRA</td>
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<tr>
<td>+ Theophylline</td>
<td>+ Oral Steroids</td>
<td>+ Others.</td>
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Step.1 Step.2 Step.3 Step.4 Step.5

One Cursory look at the above 2 guidelines will
impress upon us the uniformity of both. \(^9,3\) GINA has
shifted to levels of control which are simpler and
easier to follow than the older guidelines and this
is a clear deviation from established norms. \(^9\) The
concept of control makes it much more clinically
appealing and easier to implement. It also makes it
easy for the patient to follow and report symptoms
and avoid the usage of uncomfortable terminology.
The approach using control is very simple even to the
illiterate and easy to understand. The BTS sticks to a
step wise approach with a clear emphasis on Preventor
Therapy. \(^13\) The concept of prevention and relief is
probably under played in all guidelines and this
could be food for thought in the days to come. Such
a concept is easy both for the clinician to explain and
the patient to understand and could go a long way in
asthma control. The concept of step up and step down
appears to be reasonably uniform in all guidelines
and needs to be seriously considered by clinicians
at every step of therapy. \(^4\) We shall now consider
the usage of specific medication with reference to
guideline implementation. The necessity to include
Asthma Education as part of every guideline needs to
be emphasised at every level. \(^8\) This is more important
taking into consideration that all guidelines are clear
about the need for a certain level of self management.\(^12\)
The recent emphasis on patient related quality of life
scores becomes more relevant in this regard. \(^8\)

**ICS**

The inhaled corticosteroid forms the backbone and
foundation of asthma therapy and its introduction
has revolutionised the approach to asthma control
(3:4). The use of ICS begins with step 2 in both the
above guidelines with GINA advocating a low dose
to begin with and the BTS opting for a starting dose
of 400mcg – beclomethasone equivalent. The flip side
of mono therapy with ICS would be the reasonably
prolonged period of time necessary to achieve control.
The non availability of ICS as monotherapy could be
another hurdle to overcome. This is compounded by
the innumerable number of ICS LABA combinations
available that would result in faster asthma control.\(^3\)
GINA also has the leukotriene modifier as add on
therapy where as the BTS refrains from mentioning this.
Practically LTRAs are usually added if there is an
additional element of rhinitis and background atopy
in association with asthma. \(^10\) This could achieve better
control of both rhinitis and asthma. This concept
appears to have been well established in clinical
practice and finds a strong recommendation in the
ARIA Guidelines - Allergic rhinitis and its impact on
asthma guidelines. However one must understand
that it is not all patients who will respond to LTRAs
and hence serious consideration should be given to
withdrawing the LTRAs if there is no substantial
clinical benefit after 12weeks. \(^10\) The guidelines
do not talk about the individual inhaled steroids.
Beclothemasone has been the oldest ICS in use and
still a very useful drug, the only problem being that it
is extremely short acting and needs to be used thrice
to four times a day. Fluticasone is a good topical
anti inflammatory agent and is probably best suited
for once daily use. Budesonide is another useful ICS
preferably used twice daily with a large volume of
data available for its safety and efficacy. The concept
of single inhaler therapy for both prevention and
rescue is a simple and practical way of achieving
asthma control and this will be dealt with on the
section of LABAs. \(^5\) The side effects of inhaled steroids
are also emphasised specially in the BTS guidelines
where side effects like Blood pressure – blood sugar –
bone mineral density- growth in children need also
be monitored on a regular bass. \(^13\) The evidence for the
side effects of low dose of inhaled steroids is very
poor and it can be safely assumed in clinical practice
that doses below 800 micrograms beclomethasone
equivalent are safe. This is also compounded by the
multiplicity of medication taken and also on the
presence or the absence of oral steroids. This does
not appear to be a major problem at present. Smokers
probably will need a slightly higher dose of ICS for
adequate asthma control. \(^13\)

Inhaled steroids continue to be backbone of asthma
therapy and are powerful tools which when put to
adequate use can result in excellent asthma control. It
appears that the Inhaled steroids form the backbone
of Asthma Therapy and one of the simplest ways to
assess its efficacy would be to look at the impact of
medication on asthma related mortality. It is now
well established that long term ICS use not only gives
better asthma control but also impacts mortality.
The two short acting beta-agonists are salbutamol and terbutaline and for all practical purposes they may be considered together (9:25). There is little difference in the approach to SABAs and there is general all round agreement that this is a class of medication that needs to be used on a need oriented basis alone IE – SOS. Step one of the two guidelines makes it clear that the SABA is used specifically in step 1 as mono therapy and thereafter in all other stages as add on therapy to the existing level of treatment and used on a need oriented basis only. The indiscriminate use of SABA’s has become a major hurdle in asthma control as patients who are started on SABA’s continue to use them due to their rapid onset of action and drop the preventor medication and hence have a disastarous impact on asthma control.11 The necessity to communicate this to patient is vital and it could profoundly impact long term asthma control strategy.3 The side effects of SABA’s don’t find a clear mention in the guidelines. It will be necessary to educate patient regarding SABA related side effects especially effects like peripheral tremor tachycardia and cardiac rhythm related disturbances.

LABAs

The long acting betaagonists are another vital element in asthma control. The FACET was the first trial that started the concept of combination inhalation therapy with the addition of the LABA to ICS. To make a long story short the addition of formeterol to budesonide was better than doubling the dose of budesonide. This started a multiplicity of treatment strategies like the AMD – adjustable maintenance dosing and currently the SMART approach that propagates the use of a single inhaler for prevention and relief.13 The SMART approach simply states that a single inhaler as rescue medication along with its regular use as controller therapy will result in good asthma control.13,5 The current experience has been that this has been a useful approach in patients with stable asthma though there have been questions raised in those with unstable and brittle asthma.7 There appears to be a marginal but clear difference between salmeterol and formoterol in the sense that formoterol appears to have a dose response relationship i.e.there is better bronchodilatation on increasing the dose of formoterol in comparison with salmeterol that appears to have no dose response relationship. Also formoterol has a more rapid onset of action which facilitates its use as a reliever therapy. It clearly appears that formoterol is a more dynamic drug compared to salmeterol and hence the SMART finds a mention in the Gina guidelines.9 There are critics of the SMART approach7 and it may be revisited in the next guidelines. The SMART approach may not be taken to account that Asthma appears to be a multifaceted disease with multiple phenotypes that may not really fit the SMART approach.7 The fact does remain that LABAs are a major component of rapid asthma control and they will continue to play a pivotal role in the future. There is also caution on using LABAs as monotherapy.5 Due to its deleterious cardiovascular side effects. There is no recommendation against the use of combination inhalers – ICS LABA at this point in time (Figure 1). Safety of ICS LABA combinations
has been well established and will probably form the corner stone of asthma therapy in the future. The use of combination inhalation specially post exacerbation has been a subject of much deliberation. The ICS LABA combinations have thus undergone a transformation from the FACET to the AMD to the SMART approach and this has made asthma control goals easier to achieve. The AMD or adjustable maintenance dosing and the Smart make use of a single inhaler therapy for both prevention and relief with AMD stepping combination therapy for a couple of days till control is achieved and the SMART using the combination inhalation therapy for both prevention and relief.

The LABAs will continue to play a vital role and with the introduction of a truly once daily LABA – Indacaterol the future of LABAS - ULTRALABAS appear bright. The combination of Mometasone and indacaterol if approved for asthma could herald a new era of once daily therapy and greatly improve compliance. The expectation of once daily medication for long term asthma control has been a distant goal but it appears to be within striking distance at present.

**LTRA**

The discovery and clinical use of the leukotriene modifiers the receptor blockers like montelukast and the enzyme inhibitors like ziluton have opened up a new array of approach to a clear segment of the asthmatic population. The use of montelukast has found tremendous acceptance and efficacy in patients with concomitant allergic rhinitis and asthma and has also become popular and effective medication in the paediatric population. The safety of LTRAs has been fairly established. LTRAs are recommended at step 2 in GINA and step 3 in BTS guidelines. In both instances they are recommended as additions to ICS LABA combination. The side effects of LTRAs like depression are not so very common and are seldom seen in clinical practice. The leukotrienes are recommended to be continued further down the line in both guidelines. There are also popular medication in the paediatric population specially because of increased association between allergic rhinitis and asthma. There are however a clear set of non responders and it would be pertinent to identify these patients and withdraw the drugs at the earliest. The use of LTRA as monotherapy in established asthma is not recommended and it is always used as an add on medication to ICS-ICS/LABA.

**Theophylline**

Perhaps the most popular and widely used medication in asthma in India are the theophyllines. They act on cyclic AMP and prevent conversion of cyclic AMP to 5 – AMP thus resulting in bronchodilatation. Theophyllines are essentially weak bronchodilators but have a plethora of additive effects like diuresis, and respiratory muscle stimulant activity. A multiplicity of preparations are available including sustained release preparations which have had a mixed response in patients. Theophylline recommended at step 3 in both GINA and BTS and this is further evidence of the fact that as a group they are add on medication to primary ICS LABA combination medication. Intravenous theophylline is no longer recommended routinely as it has a very narrow therapeutic spectrum and could spill over into the toxic range producing a variety of adverse effects like restlessness, irritation and tachyarrhythmias.

The popularity of theophylline is driven by the fact that it is cheap, reasonably effective and has been around for a very long time. The limitations of Theophylline need to be taken into consideration in clinical practice. Theophylline also has multiple alternative actions that have been proclaimed but never clearly documented in large clinical trials. They include a mild diuretic effect and effect on diaphragmatic musculature. These effects are probably dose related and the concept of low dose theophylline has been propagated and is probably of some benefit in certain selected patients.

**Oral Steroids**

Oral Glucocorticoids continue to be the mainstay of severe exacerbations and are predominantly placed at step 5-in the Gina and BTS guidelines. These Guidelines do not specify the exact molecule to be used. The most commonly used oral steroid continues to be oral prednisolone, which is usually started at 5 to 10 mg daily and stepped up gradually. Steroids related side effects like muscle cramps – osteoporosis and cushingoid features are usually seen in patients who abuse steroids by using them long term usually without medical supervision. Steroids are the most effective anti inflammatory therapy available and hence are used extensively. It is always necessary to weigh the effects verses the side effects of oral steroids before prescribing them. The advent of refined steroids like Methyl prednisolone and deflazocort have probably made a marginal change in the sense that these are reported to have less steroid related side effects. It is always better to remember that oral steroids need to be used with caution and constant supervision.

**Anti IGE**

The advent of the Anti IGE monoclonal anti body – omalizumab has provided a different platform for management of asthma- this is recommended
by GINA at stage 5 – the BTS does not mention omalizumab but mentions other therapy to minimise the use of oral steroids. This therapy has so far shown moderate results in stage 5 and may be of particular use in reducing the requirement of oral steroids. The dosage of this drug is based on the level of the IGE and has a clear dosage regimen that needs to be followed taking into consideration the IGE level and the weight of the patient. The real problem with this therapy is its cost benefit ratio and with the high cost of medication this becomes a major consideration.

In conclusion Guideline based Asthma therapy enables physicians to have a practical, uniform and structured approach to asthma management. It is also pertinent that Physicians make changes in guidelines depending upon the type of practice and the demographics of patients. Ultimately the choice of medication is squarely dependent on the experience of the attending physician and his ability to adapt to local ground realities.

Experience is not what happens to you : its what you do with what happens to you

Aldous Huxley

References