

Asthma



Definition

Asthma is an inflammatory disorder of the airways characterized by cough, wheezing, chest tightness, dyspnea, and variable airflow obstruction.

Pathogenesis

The pathophysiologic mechanisms of asthma include:

- ❖ Chronic airway inflammation
- ❖ Airway narrowing due to edema
- ❖ Subepithelial fibrosis
- ❖ Smooth muscle hypertrophy,
- ❖ Mucus hypersecretion
- ❖ Airway smooth muscle constriction causing bronchial hyperreactivity in response to various stimuli.

Risk Factors

Risk factors for asthma include both **host** and **environmental** factors.

Host factors: genes predisposing to atopy; bronchial hyperreactivity; and airway inflammation have been identified.

Environmental factors:

- ❖ Exposure to indoor allergens (mites, furred animals, cockroaches, molds)
- ❖ Outdoor allergens (pollens, molds)
- ❖ Tobacco smoke
- ❖ Occupational sensitizers and allergens,
- ❖ Viral respiratory infections
- ❖ Air pollution.
- ❖ Obesity

Symptoms and Clinical Evaluation

Symptoms are :

- ❖ Intermittent and occur in response to various potential stimuli include: allergens, infections, dusts, fumes, and exercise.
- ❖ Have a diurnal variation, worsening in the evening and early morning.
- ❖ Variability of symptoms (both improvement and worsening of symptoms over time) is a key diagnostic feature of asthma.
- ❖ Symptoms often occur with or worsen with viral infection.

Common symptoms :

- ❖ Cough

- ❖ Wheezing

- ❖ Chest tightness

- ❖ Shortness of breath

Physical examination

- ❖ Wheezing
- ❖ Reduced airflow
- ❖ Prolonged expiratory phase
- ❖ Patients may also have a completely **normal** respiratory exam, particularly when they are symptom-free.

History taking should include also :

- ❖ Smoking history
- ❖ Pets exposure
- ❖ Work place exposure to dust, fumes, or particulate matter known to cause bronchial hyperreactivity.
- ❖ Personal or family history of atopy or allergic sinus disease.
- ❖ Presence of nasal polyps, sensitivity to aspirin, and wheezing is known as the "asthmatic triad"

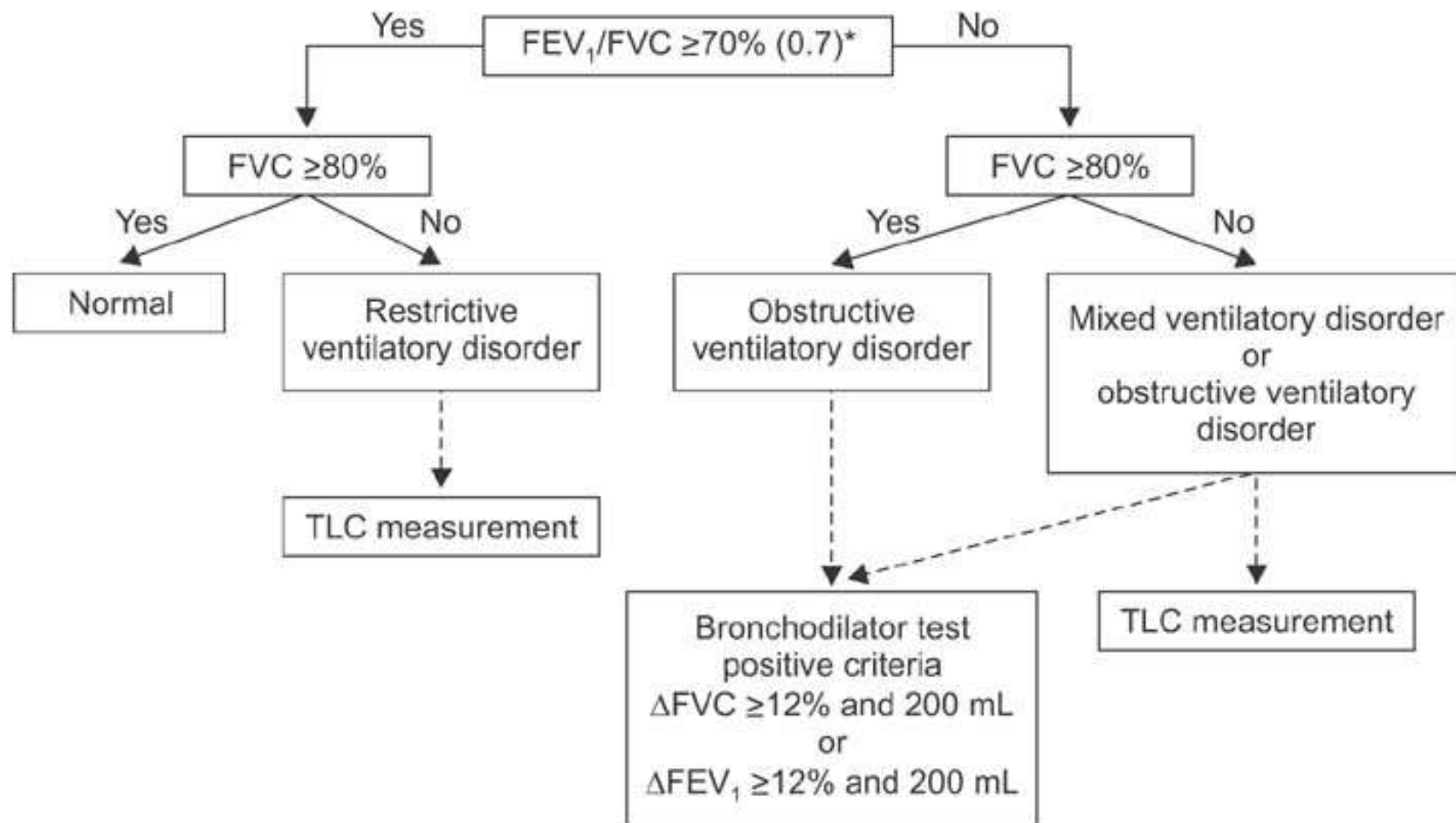
Diagnosis of asthma in low- and middle-income countries

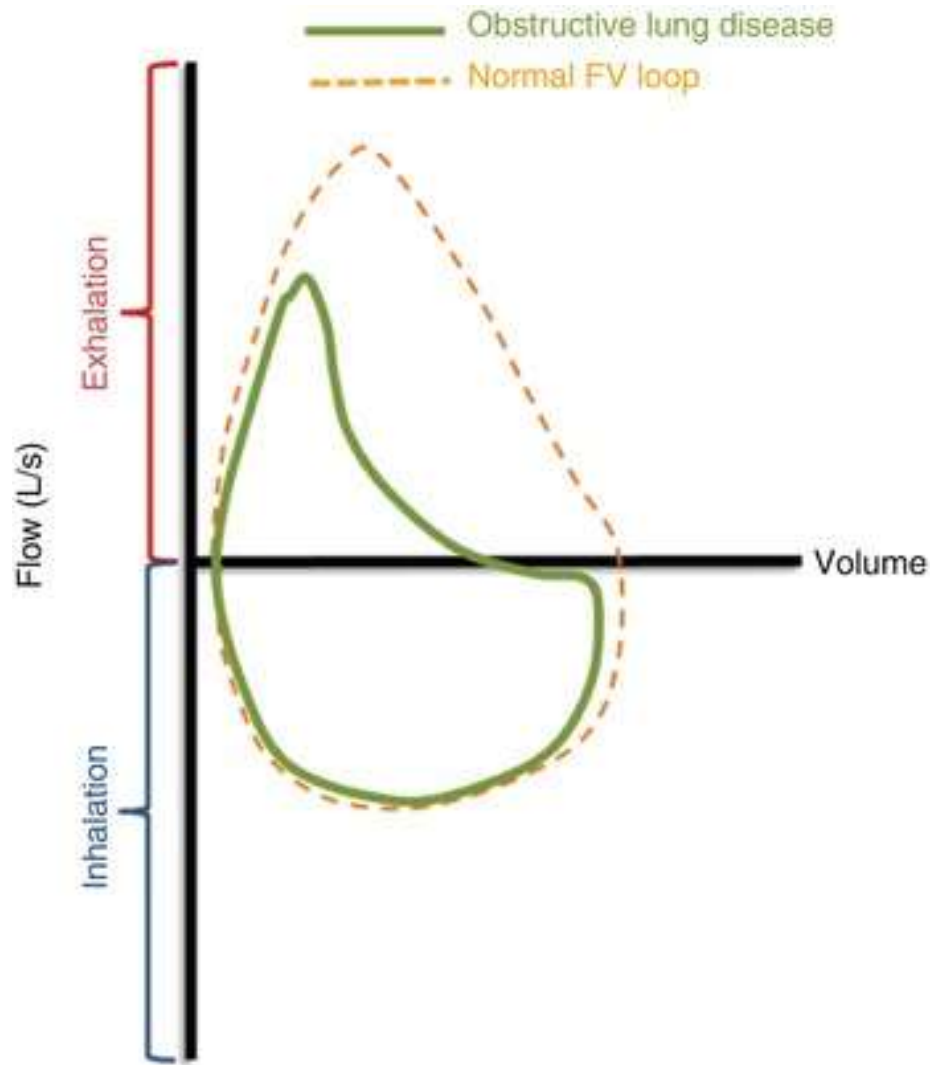


- Asthma is often under-diagnosed
 - Differential diagnosis often includes other endemic respiratory disease, e.g. tuberculosis, HIV/AIDS-associated lung disease, parasitic or fungal lung diseases
 - A syndromic approach is often used for diagnosis
- GINA recommends confirmation of asthma diagnosis with lung function testing, whenever possible, before commencing long-term treatment
 - **Spirometry-based testing if available**
 - **Peak expiratory flow (PEF)**
 - ✦ **>20% increase in PEF, 15 minutes after 2 puffs of salbutamol = asthma likely (WHO-PEN)**
 - ✦ **Improvement of symptoms and PEF after 4 weeks ICS treatment**
- Access to affordable diagnostic equipment and skills training needs to be substantially scaled up in low- and middle-income countries

Diagnosis

Confirmation of reversible airflow obstruction with bronchodilators is a cornerstone of asthma diagnosis and can be assessed by spirometry or by serial measurement of peak expiratory flow rates.





Bronchodilator reversibility :

Significant bronchodilator reversibility is defined by:
FEV₁ increases by > 200 mL **AND** >12% of the
baseline value.

It is assessed by the administration of a short acting
beta 2 agonist and repeating spirometry after around 10
minutes

Bronchial challenge test

- ❖ This is usually performed with inhaled methacholine, although other stimuli (exercise, mannitol) have been validated.
- ❖ Positive test : if there is 20% decrease in FEV₁ from the baseline
- ❖ A negative test excludes asthma
- ❖ A positive test requires clinical correlation and may require additional testing.
- ❖ In exercise challenge test: fall in FEV₁ > 10% or 200 ml from baseline

Fractional exhaled nitric oxide

Levels of inducible nitric oxide synthases (iNOS) rise in inflammatory cells and eosinophils, so levels of NO correlates with levels of inflammation.

In adults level ≥ 40 parts per billion ppb, is considered +ve

In children ≥ 35 ppb is considered +ve

Asthma Syndromes

- 1) Allergic Asthma
- 2) Cough-Variant Asthma
- 3) Exercise-Induced Bronchospasm
- 4) Occupational Asthma
- 5) Reactive Airways Dysfunction Syndrome
- 6) Aspirin-Exacerbated Respiratory Disease
- 7) Allergic Bronchopulmonary Aspergillosis

Common Comorbidities

Comorbidities in asthma are common and should be considered and actively managed to reduce symptoms and potentially improve asthma control.

- ❖ Gastroesophageal Reflux Disease
- ❖ Sinus Disease
- ❖ Obstructive Sleep Apnea
- ❖ Vocal Cord Dysfunction
- ❖ Obesity

Management of Chronic Asthma

The goals of longitudinal asthma management are :

- 1) Control chronic asthma symptoms
- 2) Prevent acute exacerbations
- 3) Minimize risks of developing fixed airway obstruction

Box 2-2. GINA assessment of asthma control in adults, adolescents and children 6–11 years

A. Asthma symptom control		Level of asthma symptom control		
In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than twice/week?	Yes ☐ No ☐	None of these	1–2 of these	3–4 of these
• Any night waking due to asthma?	Yes ☐ No ☐			
• SABA reliever for symptoms more than twice/week*?	Yes ☐ No ☐			
• Any activity limitation due to asthma?	Yes ☐ No ☐			
B. Risk factors for poor asthma outcomes				
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations. Measure FEV ₁ at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.				
Having uncontrolled asthma symptoms is an important risk factor for exacerbations. ⁸⁶				
Additional potentially modifiable risk factors for flare-ups (exacerbations), even in patients with few symptoms [†] include:				
• Medications: high SABA use (associated with increased risk of exacerbations^{123,87} and mortality particularly if $\geq 1 \times 200$-dose canister per month^{88,89}); inadequate ICS: not prescribed ICS; poor adherence;⁹⁰ incorrect inhaler technique⁹¹ • Other medical conditions: obesity;^{92,93} chronic rhinosinusitis;⁹³ GERD;⁹³ confirmed food allergy;⁹⁴ pregnancy⁹⁵ • Exposures: smoking;⁹⁶ allergen exposure if sensitized;⁹⁶ air pollution⁹⁷⁻⁹⁹ • Context: major psychological or socioeconomic problems¹⁰⁰ • Lung function: low FEV₁, especially $<60\%$ predicted^{96,101}; high BD reversibility^{93,102,103} • Other tests in patients with Type 2 inflammation: blood eosinophils;^{93,104,105} elevated FeNO (in adults with allergic asthma taking ICS)¹⁰⁶				
Other major independent risk factors for flare-ups (exacerbations)				
• Ever intubated or in intensive care unit for asthma¹⁰⁷ • ≥ 1 severe exacerbation in last 12 months^{108,109}				
Risk factors for developing persistent airflow limitation				
• History: preterm birth, low birth weight and greater infant weight gain;¹¹⁰ chronic mucus hypersecretion^{111,112} • Medications: lack of ICS treatment in patients who had a severe exacerbation¹¹³ • Exposures: tobacco smoke;¹¹¹ noxious chemicals; occupational exposures⁴⁰ • Investigations: low initial FEV₁;¹¹² sputum or blood eosinophilia¹¹²				
Risk factors for medication side-effects				
• Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors¹¹⁴ • Local: high dose or potent ICS;^{114,115} poor inhaler technique¹¹⁶				

Having any of these risk factors increases the patient's risk of exacerbations even if they have few asthma symptoms

BD: bronchodilator; FEV₁: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; OCS: oral corticosteroid; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA: short-acting beta₂-agonist. *Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise. For children 6–11 years, also refer to Box 2-3, p.37. See Box 3-8, p.74 for specific risk reduction strategies. †Independent risk factors are those that are significant after adjustment for the level of symptom control.

Term	Definition	Notes
Maintenance treatment	Asthma treatment that is prescribed for use every day (or on a regularly scheduled basis)	Medications intended to be used continuously, even when the person does not have asthma symptoms. Examples include ICS-containing medications (ICS, ICS-LABA, ICS-LABA-LAMA), as well as LTRA and biologic therapy. The term 'maintenance' describes the prescribed frequency of administration, not a particular class of asthma medicine.
Controller	Medication targeting both domains of asthma control (symptom control and future risk)	In the past, 'controller' was largely used for ICS-containing medications prescribed for regular daily treatment, so 'controller' and 'maintenance' became almost synonymous. However, this became confusing after the introduction of combination ICS-containing relievers for as-needed use. To avoid confusion, 'ICS-containing treatment' and 'maintenance treatment' have been substituted as appropriate where the intended meaning was unclear.
Reliever	Asthma inhaler taken as needed, for quick relief of asthma symptoms	Sometimes called rescue inhalers. As well as being used for symptom relief, reliever inhalers can also be used before exercise, to prevent exercise-induced asthma symptoms. Includes SABAs (e.g., salbutamol [albuterol], terbutaline, ICS-salbutamol), as-needed ICS-formoterol, and as-needed ICS-SABA. SABA-containing relievers are not intended for regular maintenance use, or to be taken when the person does not have asthma symptoms (except before exercise).

Anti-inflammatory reliever (AIR)	Reliever inhaler that contains both a low-dose ICS and a rapid-acting bronchodilator	Includes budesonide-formoterol, beclometasone-formoterol and ICS-salbutamol combinations. Patients can also use them as needed before exercise or allergen exposure to prevent asthma symptoms and bronchoconstriction. Non-formoterol LABAs in combination with ICS cannot be used as relievers. The anti-inflammatory effect of as-needed ICS-formoterol was demonstrated by reduction in FeNO in several studies.^{171,172,195} Some anti-inflammatory relievers can be used as-needed at Steps 1–2 as the person's sole asthma treatment, without a maintenance treatment ('AIR-only' treatment). Almost all evidence for this is with ICS-formoterol. Some ICS-formoterol combinations can be used as both maintenance treatment and reliever treatment at Steps 3–5 (see MART, below). For medications and doses see Box 3-15, p.80.
Maintenance-and-reliever therapy (MART)	Treatment regimen in which the patient uses an ICS-formoterol inhaler every day (maintenance dose), and also uses the same medication as needed for relief of asthma symptoms (reliever doses)	MART (Maintenance And Reliever Therapy) can be used <u>only</u> with combination ICS-formoterol inhalers such as budesonide-formoterol and beclometasone-formoterol. Other ICS-formoterol inhalers can also potentially be used, but combinations of ICS with non-formoterol LABAs, or ICS-SABA, cannot be used for MART. MART is also sometimes called SMART (single-inhaler maintenance and reliever therapy); the meaning is the same. For medications and doses see Box 3-15, p.80.

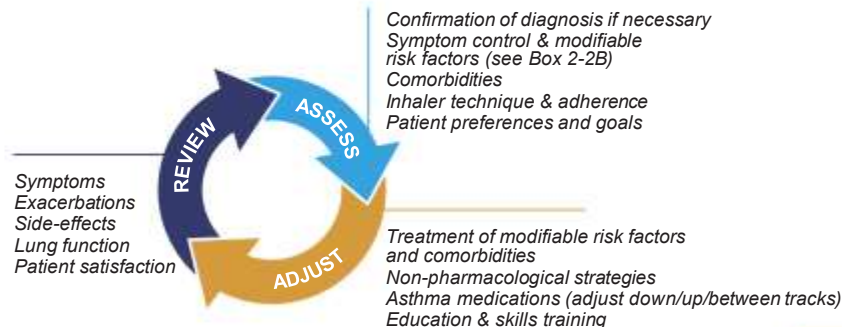
See list of abbreviations (p.10).

Presenting symptoms	Preferred INITIAL treatment (Track 1)	Alternative INITIAL treatment (Track 2)
Infrequent asthma symptoms, e.g., less than twice a month and no risk factors for exacerbations, including no exacerbations in the last 12 months (Box 2-2B, p.38)	As-needed low-dose ICS-formoterol (Evidence B)	Low-dose ICS taken whenever SABA is taken , in combination or separate inhalers (Evidence B)
Asthma symptoms or need for reliever twice a month or more	As-needed low-dose ICS-formoterol (Evidence A)	Low-dose ICS plus as-needed SABA (Evidence A). Before choosing this option, consider likely adherence with daily ICS.
Troublesome asthma symptoms most days (e.g., 4–5 days/week); or waking due to asthma once a week or more, especially if any risk factors exist (Box 2-2B, p.38)	Low-dose ICS-formoterol maintenance and reliever therapy (MART) (Evidence A)	Low-dose ICS-LABA plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B), OR Medium-dose ICS plus as-needed SABA (Evidence A) or plus as-needed ICS-SABA (Evidence B). Consider likely adherence with daily maintenance treatment.
Initial asthma presentation is with severely uncontrolled asthma, or with an acute exacerbation	Medium-dose ICS-formoterol maintenance and reliever therapy (MART) (Evidence D). A short course of oral corticosteroids may also be needed.	Medium- or high-dose ICS-LABA (Evidence D) plus as-needed SABA or plus as-needed ICS-SABA. Consider likely adherence with daily maintenance treatment. A short course of oral corticosteroids may also be needed. High-dose ICS plus as-needed SABA is another option (Evidence A) but adherence is weak compared with combination ICS-LABA.

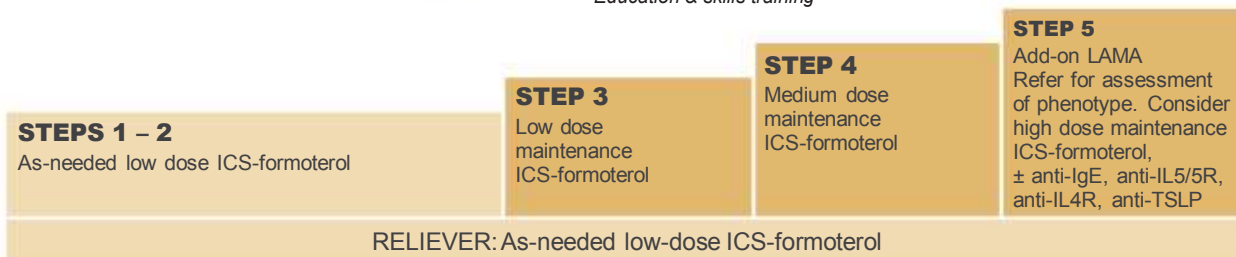
Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs

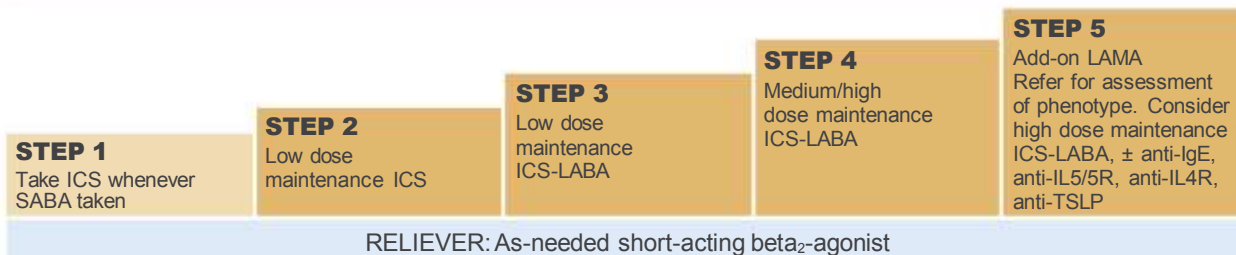


CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever



See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller



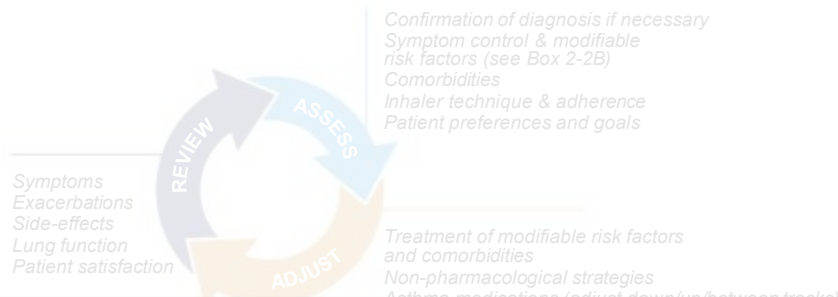
Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	Medium dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS	Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects
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Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER**
(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2

As-needed low dose ICS-formoterol

STEP 3

Low dose maintenance ICS-formoterol

STEP 4

Medium dose maintenance ICS-formoterol

STEP 5

Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

CONTROLLER and **ALTERNATIVE RELIEVER**
(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1

Take ICS whenever SABA taken

STEP 2

Low dose maintenance ICS

STEP 3

Low dose maintenance ICS-LABA

Medium/high dose maintenance ICS-LABA

Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed short-acting beta₂-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT

Medium dose ICS, or add LTRA, or add HDM SLIT

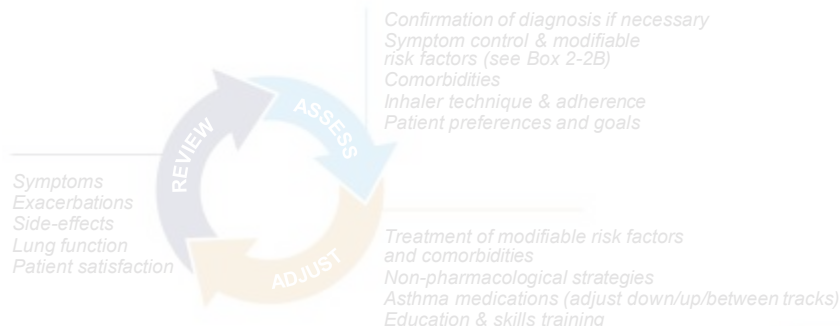
Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS

Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



CONTROLLER and
PREFERRED RELIEVER
(Track 1). Using ICS-formoterol

STEPS 1 – 2

As-needed low dose ICS-formoterol

STEP 3

Low dose
maintenance
ICS-formoterol

STEP 4

Medium dose
maintenance
ICS-formoterol

STEP 5

Add-on LAMA
Refer for assessment
of phenotype. Consider
high dose maintenance
ICS-formoterol,
± anti-IgE, anti-IL5/5R,

CONTROLLER and **ALTERNATIVE RELIEVER**

(Track 2). Before considering a
regimen with SABA reliever,
check if the patient is likely to be
adherent with daily controller

STEP 1

Take ICS whenever
SABA taken

STEP 2

Low dose
maintenance ICS

STEP 3

Low dose
maintenance
ICS-LABA

STEP 4

Medium/high
dose maintenance
ICS-LABA

STEP 5

Add-on LAMA
Refer for assessment
of phenotype. Consider
high dose maintenance
ICS-LABA, ± anti-IgE,
anti-IL5/5R, anti-IL4R,
anti-TSLP

RELIEVER: As-needed short-acting beta₂-agonist

Other controller options for either
track (limited indications, or less
evidence for efficacy or safety)

Low dose ICS whenever
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or add HDM SLIT

Medium dose ICS, or
add LTRA, or add
HDM SLIT

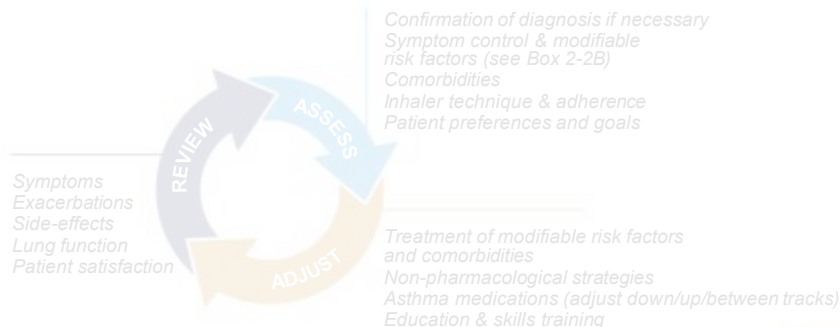
Add LAMA or LTRA or
HDM SLIT, or switch to
high dose ICS

Add azithromycin (adults) or
LTRA. As last resort consider
adding low dose OCS but
consider side-effects

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



CONTROLLER and
PREFERRED RELIEVER
(Track 1). Using ICS-formoterol
as reliever reduces the risk of
exacerbations compared with
using a SABA reliever

STEPS 1 – 2

As-needed low dose ICS-formoterol

STEP 3

Low dose
maintenance
ICS-formoterol

STEP 4

Medium dose
maintenance
ICS-formoterol

STEP 5

Add-on LAMA
Refer for assessment
of phenotype. Consider
high dose maintenance
ICS-formoterol,
± anti-IgE, anti-IL5/5R,
anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

See GINA
severe
asthma guide

CONTROLLER and
ALTERNATIVE RELIEVER

STEP 1

STEP 2

Low dose

STEP 3

Low dose
maintenance
ICS-LABA

STEP 4

Medium/high
dose maintenance
ICS-LABA

STEP 5

Add-on LAMA
Refer for assessment
of phenotype. Consider
high dose maintenance
ICS-LABA, ± anti-IgE,

Other controller options for either
track (limited indications, or less
evidence for efficacy or safety)

Low dose ICS whenever
SABA taken, or daily LTRA,
or add HDM SLIT

Medium dose ICS, or
add LTRA, or add
HDM SLIT

Add LAMA or LTRA or
HDM SLIT, or switch to
high dose ICS

Add azithromycin (adults) or
LTRA. As last resort consider
adding low dose OCS but
consider side-effects

evidence for efficacy or safety)

or add HDM SLIT

or add HDM SLIT

consider side-effects



DEFINITIONS: UNCONTROLLED, DIFFICULT-TO-TREAT AND SEVERE ASTHMA

Understanding the definitions of difficult-to-treat and severe asthma starts with the concept of uncontrolled asthma.

Uncontrolled asthma includes one or both of the following:

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
- Frequent exacerbations (≥ 2 /year) requiring OCS, or serious exacerbations (≥ 1 /year) requiring hospitalization.

*Difficult-to-treat asthma*¹⁵⁹ is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.¹⁵⁹ It does not mean a 'difficult patient'. In many cases, asthma may appear to be difficult to treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.

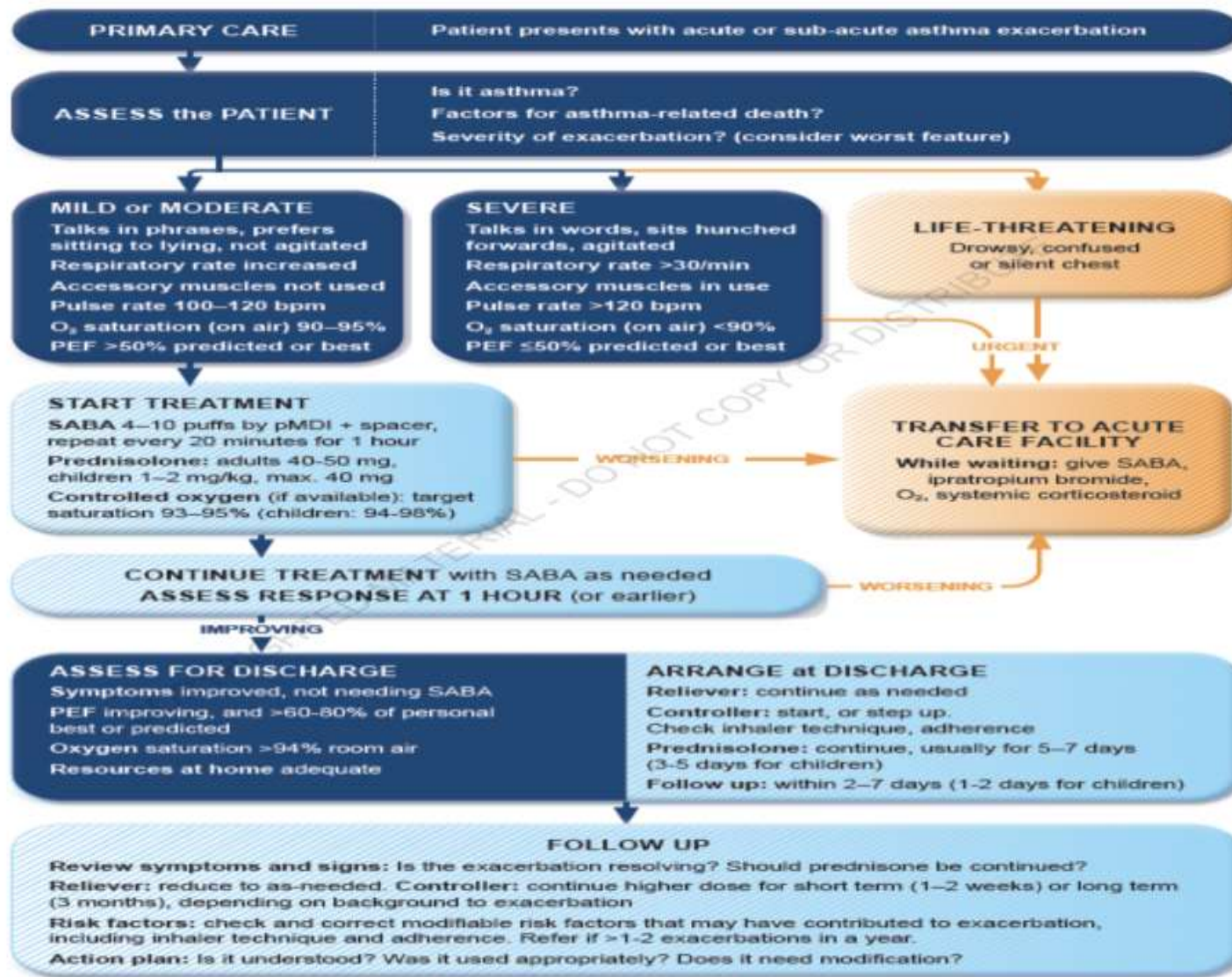
*Severe asthma*¹⁵⁹ is a subset of difficult-to-treat asthma (Box 3-15). It means asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased.¹⁵⁹ At present, therefore, 'severe asthma' is a retrospective label. It is sometimes called 'severe refractory asthma'¹⁵⁹ since it is defined by being relatively refractory to high-dose inhaled therapy. However, with the advent of biologic therapies, the word 'refractory' is no longer appropriate.

Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.¹⁵⁹

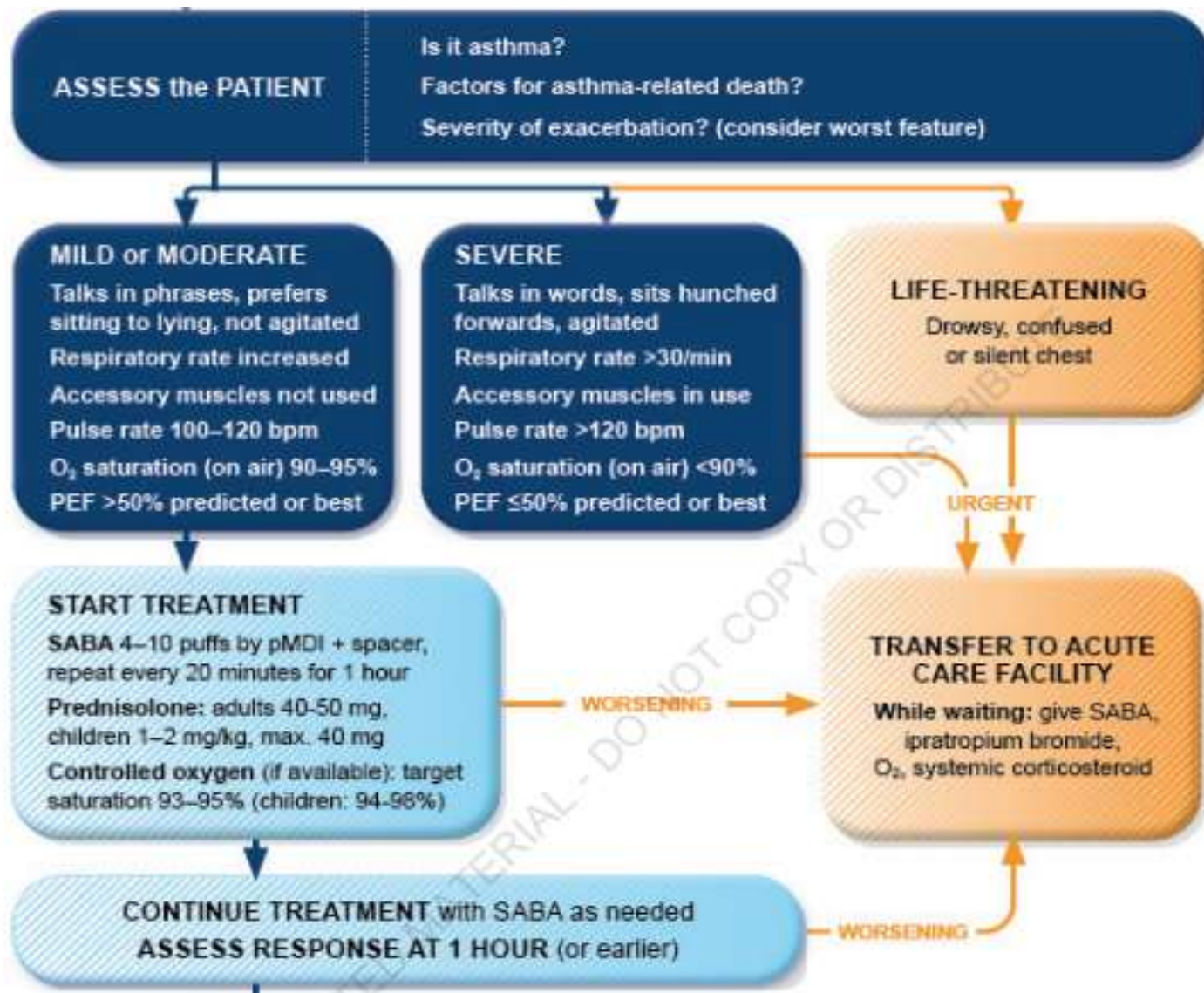
Management of Asthma Exacerbations

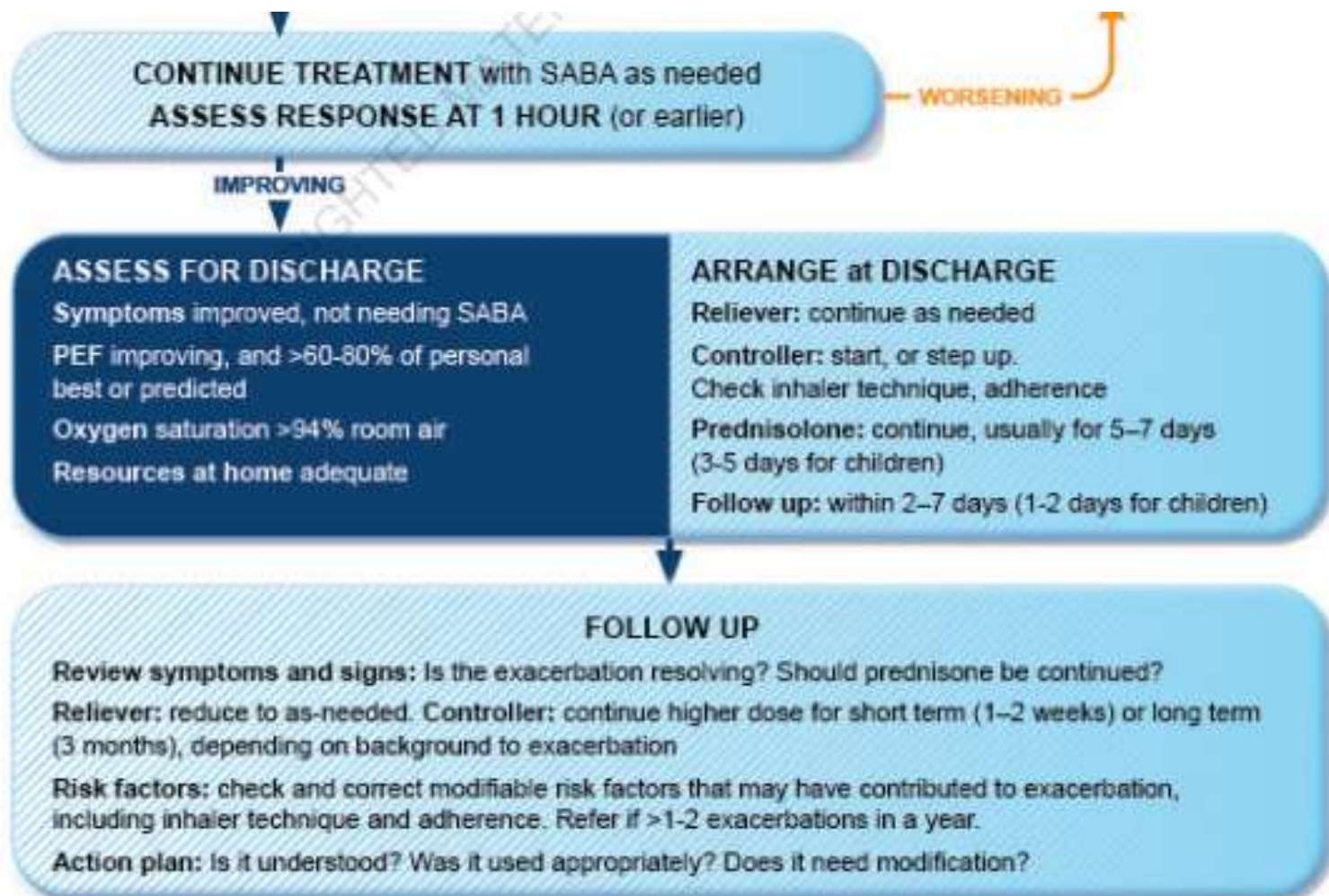
- ❖ Asthma exacerbation refers to an acute worsening in symptoms or lung function from baseline that necessitates a step-up in therapy.
- ❖ All asthma patients should have a written asthma management plan that helps them to recognize the symptoms of an exacerbation and begin self-treatment.
- ❖ Clinicians should screen for patient factors that contribute to an increased risk of death from asthma and counsel patients appropriately.

Box 4-3. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11)

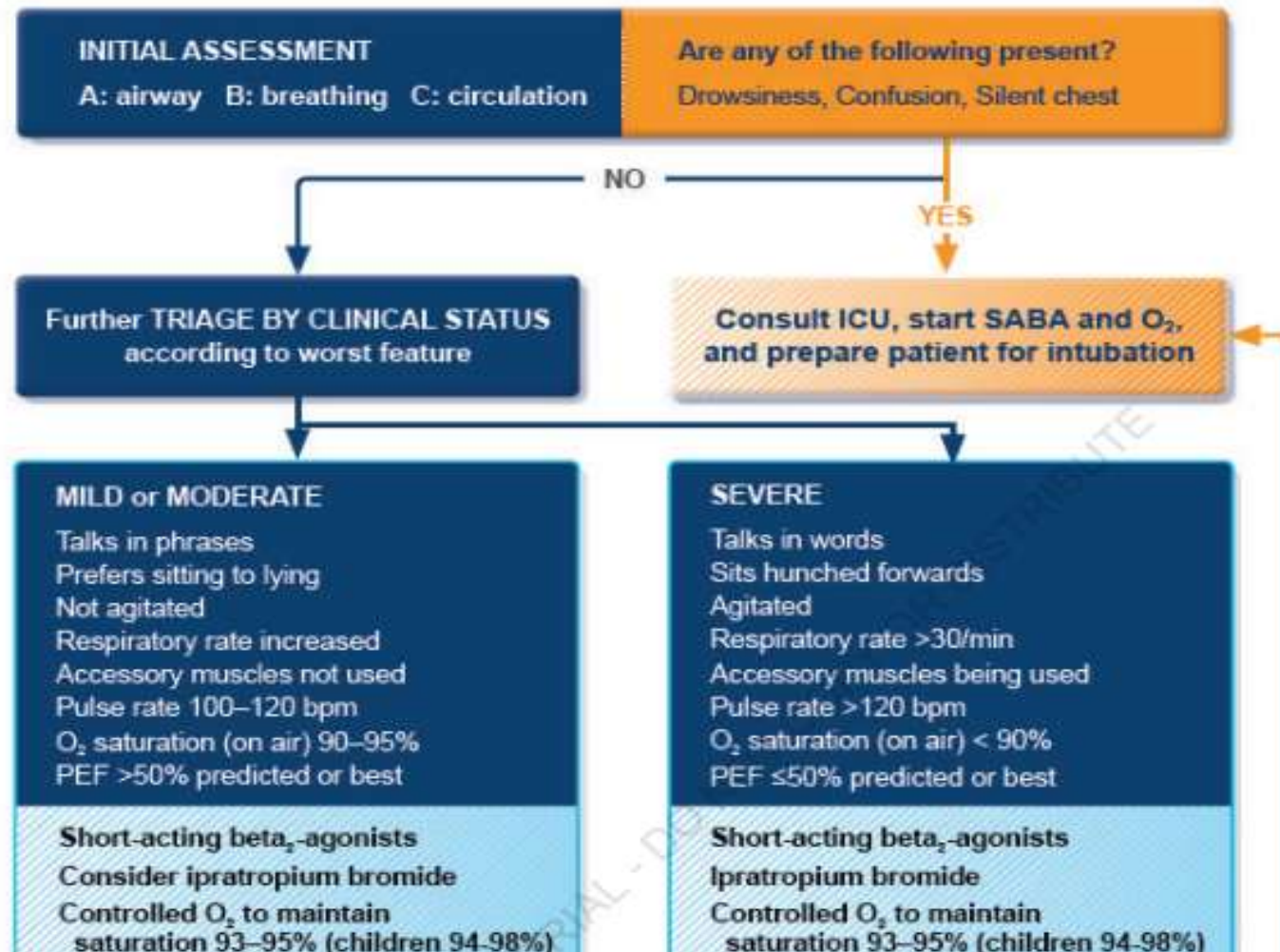


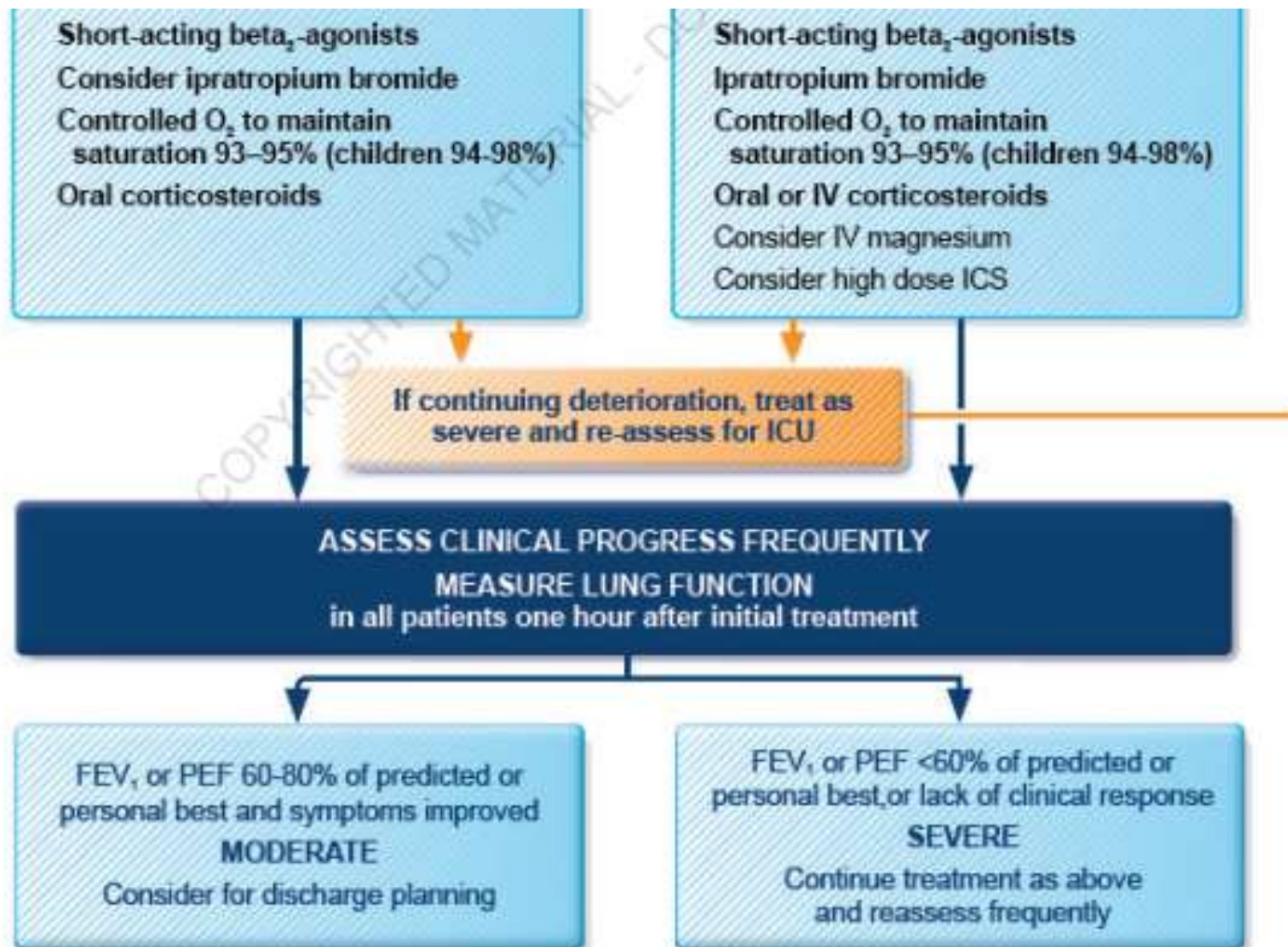
O₂: oxygen; PEF: peak expiratory flow; SABA: short-acting beta₂-agonist (doses are for salbutamol).





Box 4-4. Management of asthma exacerbations in acute care facility, e.g. emergency department





Box 4-1. Factors that increase the risk of asthma-related death

- A history of near-fatal asthma requiring intubation and mechanical ventilation⁵⁵⁷
- Hospitalization^{557,558} or emergency care visit for asthma in the past year
- Currently using or having recently stopped using oral corticosteroids (a marker of event severity)⁵⁵⁷
- Not currently using inhaled corticosteroids^{90,557}
- Over-use of SABAs, especially use of more than one canister of salbutamol (or equivalent) monthly^{89,107,559}
- Poor adherence with ICS-containing medications and/or poor adherence with (or lack of) a written asthma action plan¹⁰⁰
- A history of psychiatric disease or psychosocial problems¹⁰⁰
- Food allergy in a patient with asthma^{452,560}
- Several comorbidities including pneumonia, diabetes and arrhythmias were independently associated with an increased risk of death after hospitalization for an asthma exacerbation.^[558]

Asthma in Pregnancy

- ❖ Pregnant patients should be advised that the advantages of treatment are significantly greater than the potential risk to the fetus from asthma therapies or exacerbations.
- ❖ Pregnancy can affect asthma control, leading to either worsening or improvement, and patients should be closely monitored for signs of exacerbation, which occurs most frequently during the second trimester.
- ❖ Inhaled glucocorticoids, oral glucocorticoids, SABAs, leukotriene-receptor antagonists (montelukast, zafirlukast), and LABAs have **ALL** been used extensively during pregnancy without data to suggest fetal harm.