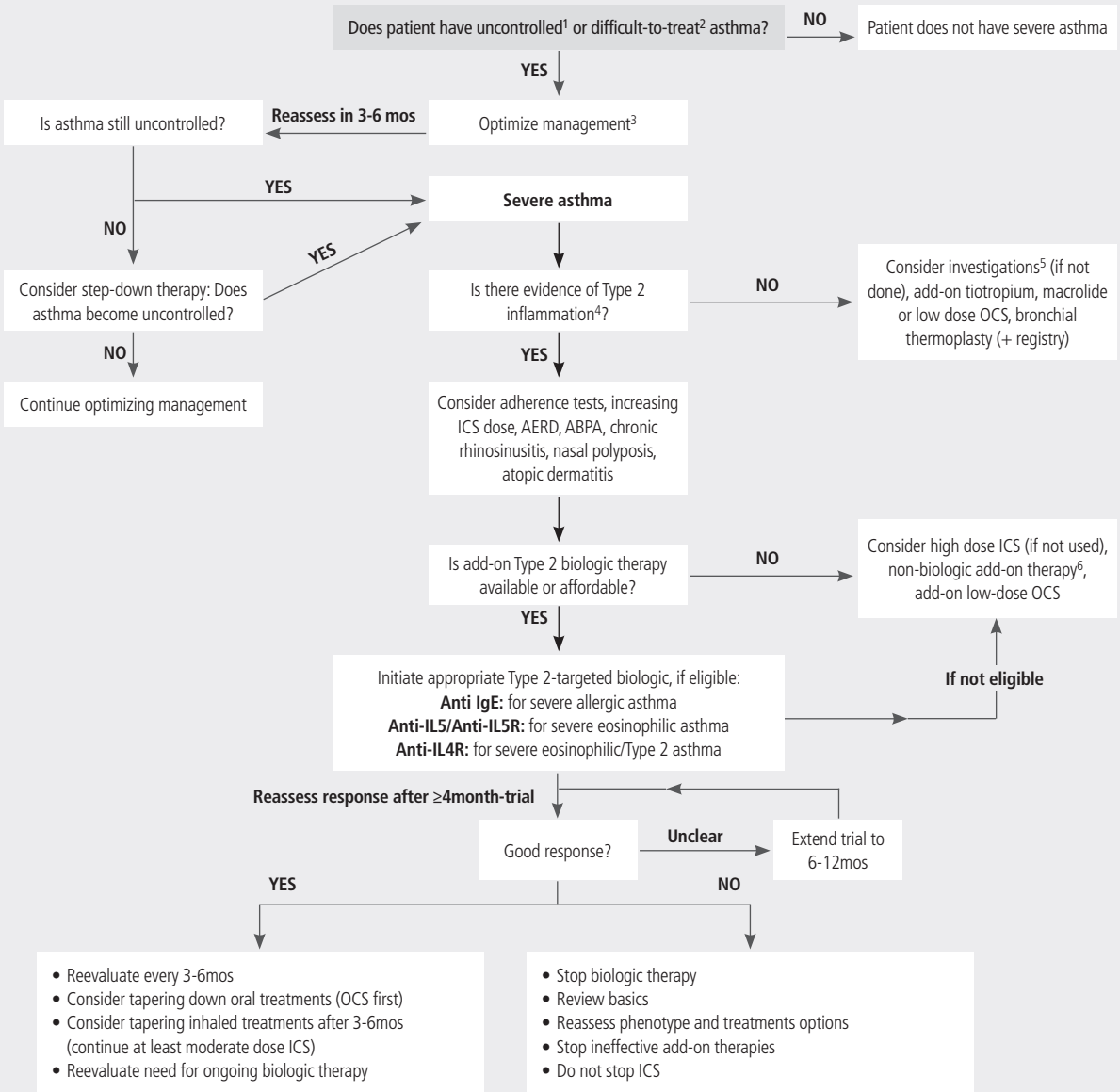
SEVERE ASTHMA MANAGEMENT (Part 1 of 3)

An estimated 3.7% of asthma patients have severe asthma. Throughout the process of diagnosis, treatment, and follow-up, it is imperative to always 1) investigate for comorbidities, differential diagnoses, and refer to specialists as appropriate, 2) stop ineffective add-on therapies, and 3) confirm absence of modifiable factors (incorrect inhaler technique, poor adherence, smoking or comorbidities).



GINA ASTHMA TREATMENT GUIDELINES

	STEP 1		STEP 2		STEP 3		STEP 4		STEP 5	
	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs
Preferred controller		PRN low dose ICS-formoterol[7]	Daily low dose ICS	Daily low dose ICS or PRN low dose ICS-formoterol[7]	Low dose ICS-LABA or medium dose ICS	Low dose ICS-LABA	Medium dose ICS-LABA. Refer to expert advice	Medium dose ICS-LABA	Refer for phenotypic assessment ± add-on therapy (eg, anti-IgE)	High dose ICS-LABA. Phenotypic assessment ± add-on therapy[8]
Other controller	Low dose ICS taken whenever SABA is taken[9], or daily low dose ICS	Low dose ICS taken whenever SABA is taken[9]	Daily LTRA or low dose ICS taken whenever SABA is taken[9]	Daily LTRA or low dose ICS taken whenever SABA is taken[9]	Low dose ICS + LTRA	Medium dose ICS or low dose ICS + LTRA[10]	High dose ICS-LABA, or add-on tiotropium, or add-on LTRA	High dose ICS, add-on tiotropium, or add-on LTRA[10]	Add-on anti-IL5, or add-on low dose OCS, but consider side-effects	Add-on low dose OCS, but consider side-effects

(continued)

GINA ASTHMA TREATMENT GUIDELINES (continued)

	STEP 1		STEP 2		STEP 3		STEP 4		STEP 5	
	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs
Preferred reliever	PRN SABA	PRN low dose ICS-formoterol[7]	PRN SABA	PRN low dose ICS-formoterol[7]	PRN SABA	PRN low dose ICS-formoterol for patients prescribed maintenance and reliever therapy	PRN SABA	PRN low dose ICS-formoterol for patients prescribed maintenance and reliever therapy	PRN SABA	PRN low dose ICS-formoterol for patients prescribed maintenance and reliever therapy
Other reliever		PRN SABA		PRN SABA		PRN SABA		PRN SABA		PRN SABA

PHARMACOLOGICAL TREATMENTS FOR SEVERE ASTHMA

INHALED CORTICOSTEROIDS

		Low (mcg)[11]		Medium (mcg)[11]		High (mcg)[11]		Notes
		6–11yrs	≥12yrs	6–11yrs	≥12yrs	6–11yrs	≥12yrs	
beclomethasone dipropionate (standard particle)	MDI	100–200	200–500	>200–400	>500–1000	>400	>1000	The choice of medication, device, and dose for each individual patient should be based on assessment of symptom control, risk factors, patient preference, and practical issues (eg, cost, ability to use the device, adherence). Once good symptom control has been maintained for 3mos, carefully titrate ICS dose to the minimum dose that will maintain symptom control and minimize exacerbation risk while reducing potential side-effects.
beclomethasone dipropionate (extrafine particle)	MDI	50–100	100–200	>100–200	>200–400	>200	>400	
budesonide	DPI	100–200	200–400	>200–400	>400–800	>400	>800	
ciclesonide	MDI	80	80–160	>80–160	>160–320	>160	>320	
fluticasone furoate	DPI	50	100	50	100	—	200	
fluticasone propionate	DPI	50–100	100–250	>100–200	>250–500	>200	>500	
	MDI	50–100	100–250	>100–200	>250–500	>200	>500	
mometasone furoate	DPI	—	200	—	200	—	400	
	MDI	100	200–400	100	200–400	200	>400	

BIOLOGICS

Generic	Brand	Strength	Dosing	Notes
Anti-IgE				
omalizumab	**Xolair**	75mg/0.5mL, 150 mg/mL; 150mg/vial	**<6yrs: Not established. ≥6yrs:** Base dose and frequency on baseline serum total IgE level and body weight. Give by SC inj over 5–10secs. 75–375mg every 2 or 4wks; max 150mg per inj site.	**Trial duration:** ≥4mos **Eligibility:** sensitization to inhaled allergen, AND total serum IgE and body weight within local range, AND more than a specified number of exacerbations within the last year **Predictors of (+) response:** blood eosinophils ≥260/μL or FeNO ≥20ppb, allergen-driven symptoms, childhood-onset asthma
Anti-IL5/5R				
mepolizumab	**Nucala**	100mg/mL, 100 mg/vial	**<6yrs: Not established. 6–11yrs** (use vials only): 40mg SC once every 4wks. **≥12yrs:** 100mg SC once every 4wks.	**Trial duration:** ≥4mos **Eligibility:** more than a specified number of severe exacerbations within the last year, AND blood eosinophils ≥300/μL **Predictors of (+) response:** higher blood eosinophils, higher number of severe exacerbations in previous year, adult-onset asthma, nasal polyposis, maintenance OCS at baseline
benralizumab	**Fasenra**	30mg/mL	**<12yrs: Not established. ≥12yrs:** 30mg SC once every 4wks for the first 3 doses, then once every 8wks thereafter.	
reslizumab	**Cinqair**	100mg/10mL	**<18yrs: Not established. ≥18yrs:** Give by IV infusion over 20–50mins. 3mg/kg once every 4wks.	
Anti-IL4R				
dupilumab	**Dupixent**	200mg/1.14mL, 300mg/2mL	**<12yrs: Not established. ≥12yrs:** Initially 400mg (two 200mg inj at different sites) SC followed by 200mg every other week; or, initially 600mg (two 300mg inj at different sites) followed by 300mg every other week. For those with oral corticosteroids-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis for which Dupixent is indicated: initially 600mg followed by 300mg every other week.	**Trial duration:** ≥4mos **Eligibility:** more than a specified number of severe exacerbations within the last year, AND blood eosinophils ≥300/μL or FeNO ≥25ppb, OR requirement for maintenance OCS **Predictors of (+) response:** higher blood eosinophils, higher FeNO
INHALED CORTICOSTEROIDS + LONG-ACTING BETA$_2$-ANTAGONIST				
budesonide/ formoterol	**Symbicort**	80mcg/4.5mcg, 160mcg/4.5mcg	**<6yrs: Not established. 6–<12yrs:** 2 inh of 80/4.5 twice daily (approx. 12hrs apart). **≥12yrs:** Initially 2 inh of 80/4.5 or 160/4.5 twice daily (approx. 12hrs apart), based on asthma severity. If inadequate response after 1–2wks using 80/4.5 strength, may switch to 160/4.5 strength. Max 2 inh of 160/4.5 twice daily.	Prime by shaking (5 secs) and spraying inhaler 2 times. Discard 3mos after opening foil pouch.
fluticasone furoate/ vilanterol	**Breo Ellipta**	100mcg/25mcg, 200mcg/25mcg	**≤17yrs: Not established. ≥18yrs:** Initially 1 inh of 100/25mcg or 200/25mcg once daily, based on disease severity and previous asthma therapy. Max 1 inh of 200/25mcg once daily.	Discard 6wks after opening foil tray.

(continued)

SEVERE ASTHMA MANAGEMENT (Part 3 of 3)

INHALED CORTICOSTEROIDS + LONG-ACTING BETA$_2$-ANTAGONIST (continued)

fluticasone propionate/ salmeterol	**Advair HFA**	45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	**<12yrs: Not established** **≥12yrs:** Initially 2 inh of 45/21 or 115/21 or 230/21 twice daily (approx. 12hrs apart), based on disease severity and previous asthma therapy. If inadequate response after 2wks, use next higher strength. Max 2 inh of 230/21 twice daily.	Prime by shaking (5 secs) and spraying inhaler 4 times.
	Advair Diskus	100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg	**<4yrs: Not established.** **4–11yrs:** 1 inh of 100/50 twice daily (approx. 12hrs apart). **≥12yrs:** Initially 1 inh of 100/50 or 250/50 or 500/50 twice daily (approx. 12hrs apart), based on disease severity and previous asthma therapy. If inadequate response after 2wks, use next higher strength. Max 1 inh of 500/50 twice daily.	Discard 1 month after opening foil pouch.
mometasone furoate/ formoterol	**Dulera**	50mcg/5mcg, 100mcg/5mcg, 200mcg/5mcg	**<5yrs: Not established.** **5–<12yrs:** 2 inh of 50mcg/5mcg twice daily (AM & PM); max 200mcg/20mcg daily. **≥12yrs:** Initially 2 inh of 100mcg/5mcg or 200mcg/5mcg twice daily (AM & PM), based on disease severity and previous asthma therapy. If inadequate response after 2wks, may increase dose. Max 2 inh of 200mcg/5mcg twice daily (800mcg/20mcg per day).	Prime by shaking and spraying inhaler 4 times.

LEUKOTRIENE RECEPTOR ANTAGONIST/LEUKOTRIENE MODIFIER

montelukast	**Singulair**	4mg, 5mg chew tabs 4mg granules 10mg tabs	**<12mos: Not established. 12–23mos:** 4mg granule packet once daily in PM. **2–5yrs:** 4mg chew tab or granule packet once daily in PM. **6–14yrs:** 5mg chew tab once daily in PM. **≥15yrs:** 10mg tab once daily in PM.	Take granules by mouth within 15mins of opening packet; may dissolve in 5mL of cold or room temperature baby formula or breast milk, or mix in spoonful of soft applesauce, carrots, rice, or ice cream.
zafirlukast	**Accolate**	10mg, 20mg	**<5yrs: Not established. 5–11yrs:** 10 mg twice daily. **≥12yrs:** 20mg twice daily.	Take 1hr before or 2hrs after meals.
zileuton	**Zyflo**	600mg	**<12yrs: Not recommended. ≥12yrs:** 600mg four times daily; max 2400mg/day. **CR:** 1200mg twice daily; max 2400mg/day.	Take with meals and at bedtime. CR: take within 1hr after AM and PM meals; swallow whole.
	Zyflo CR			

LONG-ACTING ANTICHOLINERGIC

tiotropium	**Spiriva Respimat**	1.25mcg/actuation	**<6yrs: Not established. ≥6yrs:** 2 inh of Spiriva Respimat 1.25mcg/actuation (2.5mcg) once daily; max 2 inh/24hrs.	Prime by inserting cartridge into inhaler and actuating until aerosol cloud is visible; repeat 3 more times. Discard 3mos after first use.

SHORT-ACTING BETA$_2$-AGONIST

albuterol	**ProAir Digihaler**	90mcg/inh	**<4yrs: Not established. ≥4yrs:** 2 inh every 4–6hrs as needed; 1 inh every 4hrs may suffice in some patients	Does not require priming. Do not use with a spacer or volume holding chamber. Discard 13mos after opening foil pouch.
	ProAir HFA			Prime by shaking and spraying inhaler 3 times.
	ProAir Respiclick			Does not require priming. Do not use with a spacer or volume holding chamber. Discard 13mos after opening foil pouch.
	Proventil HFA			Prime by shaking and spraying inhaler 4 times.
	Ventolin HFA			Prime by shaking and spraying inhaler 4 times. Discard 12mos after opening foil pouch.

NOTES

Key: **ABPA** = allergic bronchopulmonary aspergillosis; **AERD** = aspirin-exacerbated respiratory disease; **DPI** = dry powder inhaler; **FeNO** = fractional concentration of exhaled nitric oxide; **GINA** = Global Initiative for Asthma; **ICS** = inhaled corticosteroid; **inh** = inhalation; **inj** = injection; **IgE** = immunoglobulin E; **IL** = interleukin; **LABA** = long-acting beta2-antagonist; **LM** = leukotriene modifier; **LTRA** = leukotriene receptor antagonist; **MDI** = metered dose inhaler; **OCS** = oral corticosteroid; **ppb** = parts per billion; **PRN** = as needed; **SABA** = short-acting beta$_2$-agonist

[1] Uncontrolled asthma is defined by 1) poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking), AND/OR 2) frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalization.

[2] Difficult-to-treat asthma is defined by 1) patient uncontrolled despite GINA Step 4 or Step 5 treatment, OR 2) patient requires GINA Step 4 or Step 5 treatment to maintain good symptom control and reduce risk of exacerbation.

[3] Optimize management by 1) optimizing Step 4 or Step 5 treatment (correct inhaler technique and adherence, switch to ICS-formoterol maintenance and reliever therapy), 2) treat comorbidities and modifiable risk factors, 3) consider non-biologic and non-pharmacologic interventions, 4) consider trial of high dose ICS, if not used.

[4] Evidence of type 2 inflammation includes 1) blood eosinophil ≥150/µL, AND/OR 2) FeNO ≥20 ppb, AND/OR 3) sputum eosinophil ≥2%, AND/OR 4) asthma is clinically allergy-driven, AND/OR 5) need for maintenance OCS.

[5] Includes sputum induction, high resolution chest CT, bronchoscopy for alternative/additional diagnoses.

[6] Non-biologic add-on therapy includes tiotropium, macrolide, LABA, LM/LTRA.

[7] Data only available for budesonide-formoterol.

[8] Add-on therapy: tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R.

[9] 6–11yrs: separate ICS and SABA inhalers; ≥12yrs: separate or combination ICS and SABA inhalers.

[10] Consider adding house dust mite SL immunotherapy for sensitized patients with allergic rhinitis and FEV1 >70% predicted.

[11] Suggested total daily doses for the low, medium, and high dose ICS therapies based on available studies and product information.

REFERENCE

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management And Prevention, 2020. Available from www.ginasthma.org. Accessed July 1, 2020.
Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2017;390:659-68.

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