

Global Initiative for Asthma (GINA)

What's new in GINA 2019?



GINA Global Strategy for Asthma Management and Prevention

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About the GINA strategy

- The GINA report is not a guideline, but an integrated evidence-based strategy focusing on translation into clinical practice
- Recommendations are framed, not as answers to isolated PICOT questions, but as part of an integrated strategy, in relation to:
 - The GINA goals of preventing asthma deaths and exacerbations, as well as improving symptom control
 - Current understanding of underlying disease processes
 - Human behavior (of health professionals and patients/carers)
 - Implementation in clinical practice
 - Global variation in populations, health systems and medication access
- For new therapies, 2 good quality studies + indication by EMA/FDA are required
 - For existing medications with established safety profile, GINA may sometimes make off-label recommendations for new indications (e.g. macrolides for severe asthma)



Background to changes in 2019 - the risks of 'mild' asthma

- Patients with apparently mild asthma are at risk of serious adverse events
 - 30–37% of adults with acute asthma
 - 16% of patients with near-fatal asthma
 - 15–20% of adults dying of asthma } had symptoms less than weekly in previous 3 months (*Dusser, Allergy 2007*)
- Exacerbation triggers are variable (viruses, pollens, pollution, poor adherence)
- Inhaled SABA has been first-line treatment for asthma for 50 years
 - This dates from an era when asthma was thought to be a disease of bronchoconstriction
 - Patient satisfaction with, and reliance on, SABA treatment is reinforced by its rapid relief of symptoms, its prominence in ED and hospital management of exacerbations, and low cost
 - Patients commonly believe that “*My reliever gives me control over my asthma*”, so they often don't see the need for additional treatment

Background to changes in 2019 - the risks of SABA-only treatment



- Regular or frequent use of SABA is associated with adverse effects
 - β -receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (*Hancox, Respir Med 2000*)
 - Increased allergic response, and increased eosinophilic airway inflammation (*Aldridge, AJRCCM 2000*)
- Higher use of SABA is associated with adverse clinical outcomes
 - Dispensing of ≥ 3 canisters per year (average 1.7 puffs/day) is associated with higher risk of emergency department presentations (*Stanford, AAI 2012*)
 - Dispensing of ≥ 12 canisters per year is associated with higher risk of death (*Suissa, AJRCCM 1994*)



The 12-year history behind changes in GINA 2019

- Since 2007, GINA has been actively seeking interventions for mild asthma
 - to reduce the risk of asthma-related exacerbations and death
 - to provide consistent messaging about the goals of asthma treatment, including prevention of exacerbations, across the spectrum of asthma severity
 - to avoid establishing patient reliance on SABA early in the course of the disease
- GINA emphasized poor adherence as a modifiable risk factor for exacerbations
 - When the reliever is SABA, poor adherence with maintenance controller exposes the patient to risks of SABA-only treatment
- GINA members repeatedly sought funding for RCTs of as-needed ICS-formoterol for risk reduction in mild asthma
 - Eventually culminated in 2014 with the initiation of the SYGMA studies, published in 2018 (*O'Byrne NEJMed 2018; Bateman NEJMed 2018*)



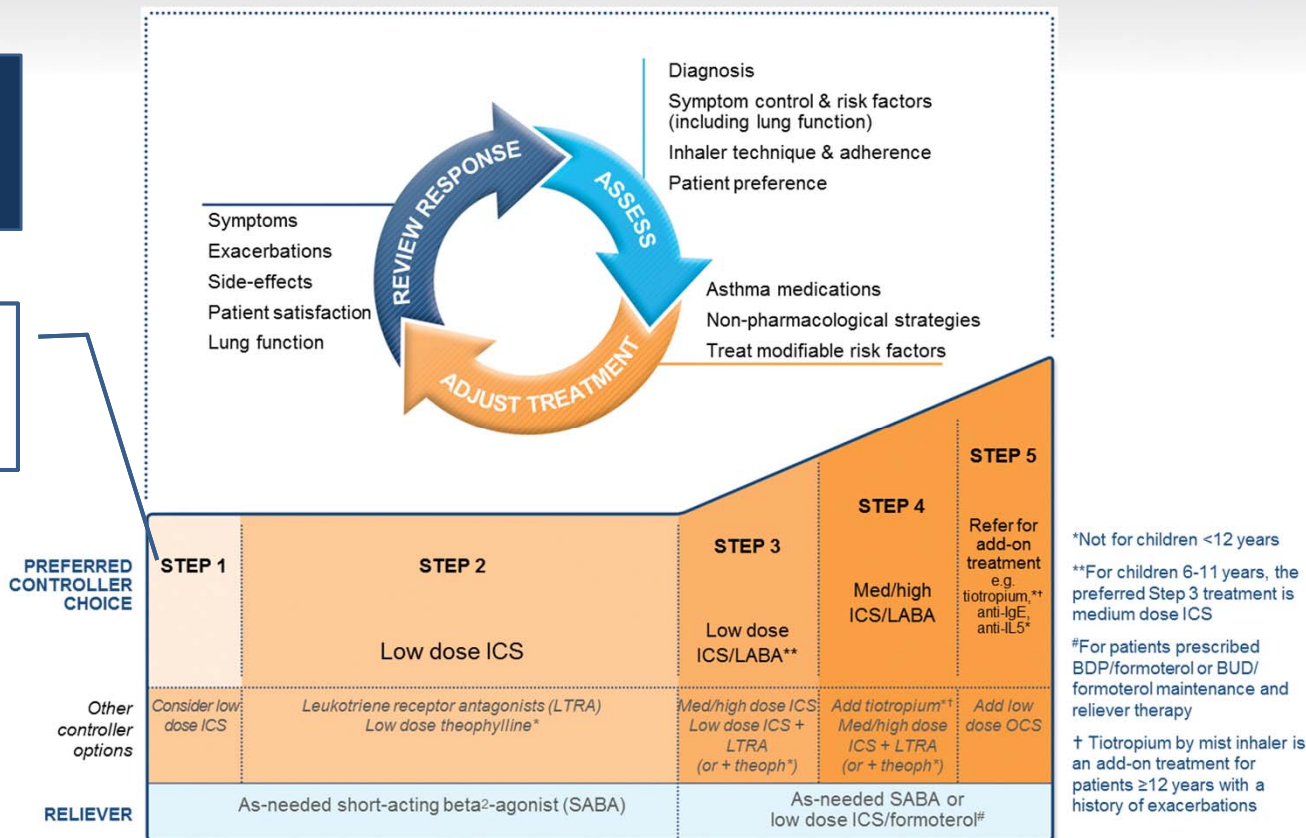
The 12-year history behind changes in GINA 2019

- In the meantime, GINA challenged conventional criteria for initiation of ICS
 - During preparation for 2014 GINA revision, we identified no evidence for the recommendation to withhold ICS until symptoms were more than twice weekly
 - This was investigated in a *post hoc* analysis of START data (*Pauwels, Lancet 2003*). This found that ICS halved the risk of serious exacerbations even in patients with symptoms 0-1 days a week at entry (*Reddel, Lancet 2017*)
- GINA found no evidence to support a Step 1 SABA-only recommendation
 - The lack of evidence for SABA-only treatment contrasted with the strong evidence for safety, efficacy and effectiveness of treatments recommended in Steps 2-5
 - In 2014, as an interim safety measure, GINA restricted SABA-only treatment to patients with symptoms less than twice a month and no risk factors for exacerbations
- 2018: Review of evidence for mild asthma, including SYGMA studies
 - A careful review of GINA conflict of interest processes was undertaken first

GINA 2018 – main treatment figure

Step 1 treatment is for patients with symptoms <twice/month and no risk factors for exacerbations

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was 'preferred'



GINA 2019 – landmark changes in asthma management

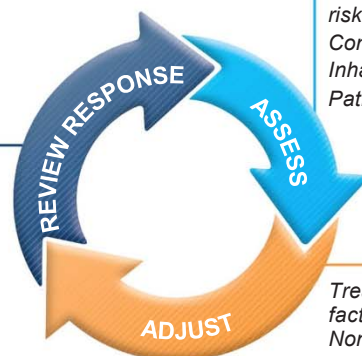


- For safety, GINA no longer recommends SABA-only treatment for Step 1
 - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
- GINA now recommends that all adults and adolescents with asthma should receive symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations
 - This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives



Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

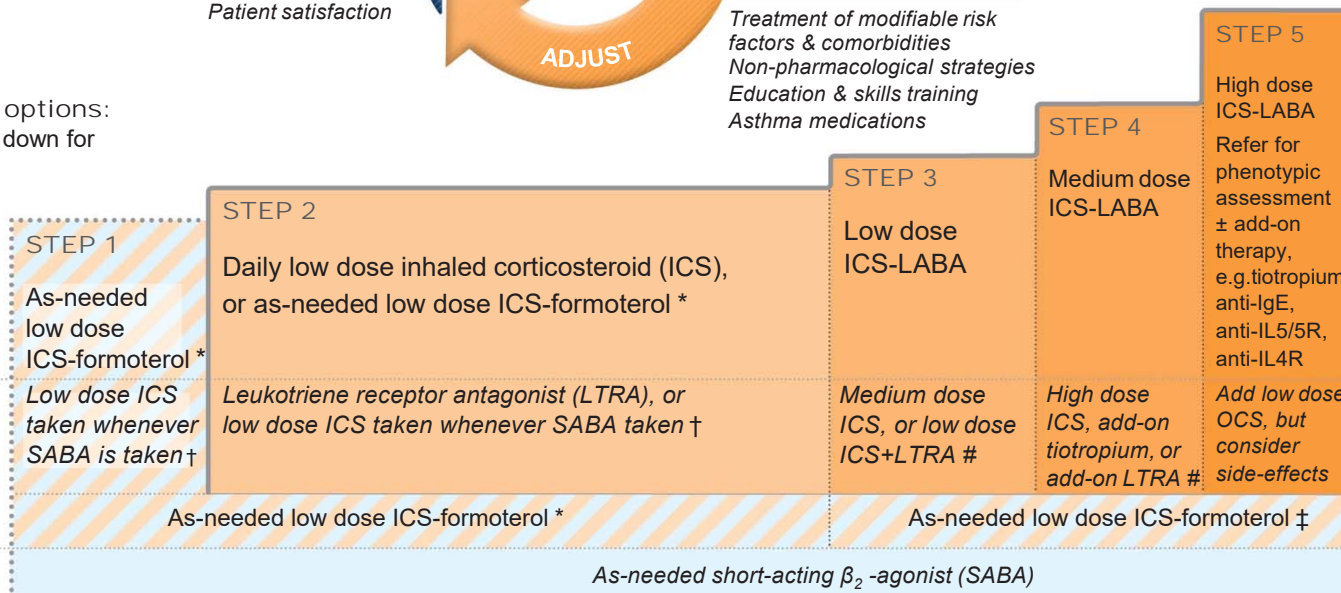
Asthma medication options:
Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option



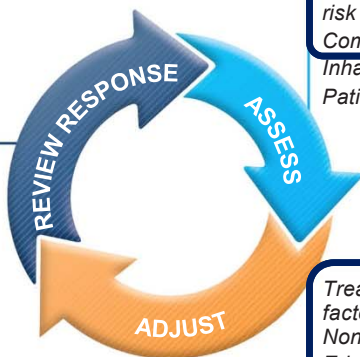
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‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted

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Adults & adolescents 12+ years

Personalized asthma management:
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Confirmation of diagnosis if necessary
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Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Asthma medication options:
Adjust treatment up and down for individual patient needs

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER	As-needed low dose ICS-formoterol*	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol*	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA
Other controller options	Low dose ICS taken whenever SABA is taken†	Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †	Medium dose ICS, or low dose ICS+LTRA #	High dose ICS, add-on tiotropium, or add-on LTRA #	Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
PREFERRED RELIEVER	As-needed low dose ICS-formoterol*		As-needed low dose ICS-formoterol ‡		
Other reliever option	As-needed short-acting β ₂ -agonist (SABA)				

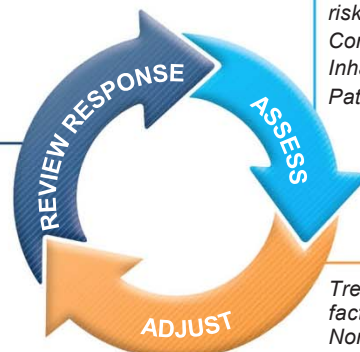
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Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted



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Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



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Patient goals

Symptoms
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Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

'Controller' treatment means the treatment taken to prevent exacerbations

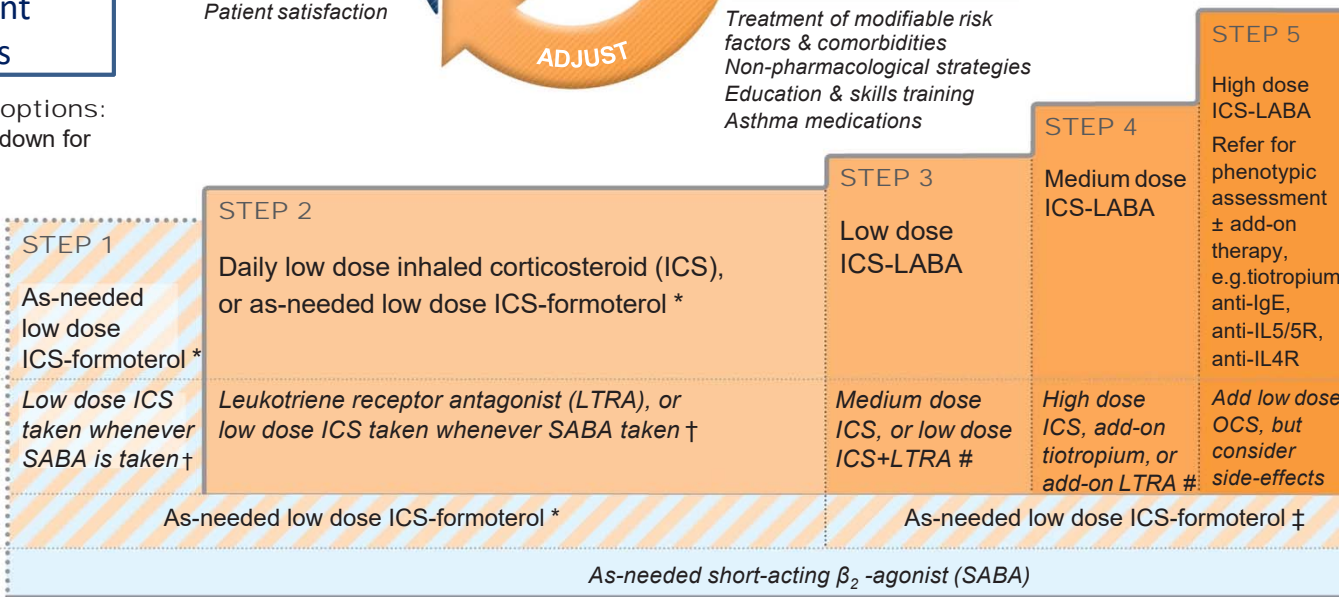
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Other reliever option



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Step 2 – rationale for changes in GINA 2019



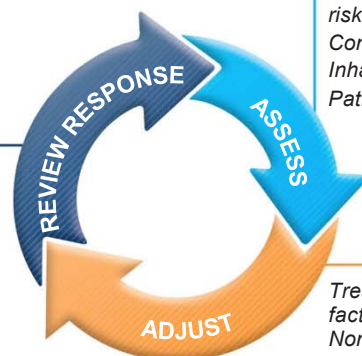
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Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
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Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

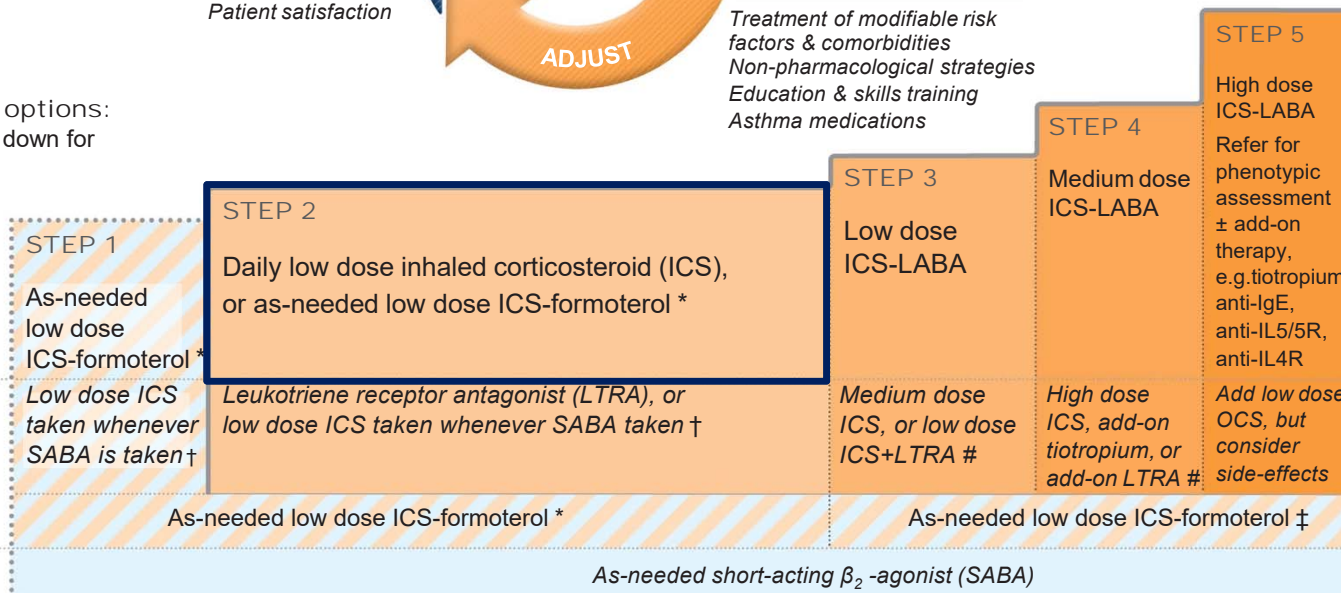
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Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted

Step 2 – there are two ‘preferred’ controller options



Regular low dose ICS with as-needed SABA

■ Evidence

- A large body of evidence from RCTs and observational studies that low dose ICS substantially reduces risks of severe exacerbations, hospitalizations and death e.g. *Suissa, NEJMed 2000; Suissa, Thorax 2002; Pauwels, Lancet 2003; O’Byrne, AJRCCM 2001*
- Serious exacerbations halved even in patients with symptoms 0-1 days per week (*Reddel, Lancet 2017*)
- Improved symptom control and reduced exercise-induced bronchoconstriction

■ Values and preferences

- High importance was given to preventing asthma deaths and severe exacerbations
- However, we were aware that poor adherence is common in mild asthma in the community, and that this would expose patients to the risks of SABA-only treatment

Step 2 – two ‘preferred’ controller options



As-needed low dose ICS-formoterol (off-label; all evidence with budesonide-formoterol)

■ Evidence

- Direct evidence from two large studies of non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA (*O'Byrne, NEJMed 2018, Bateman, NEJMed 2018*)
- Direct evidence from one large study of 64% reduction in severe exacerbations vs SABA-only treatment (*O'Byrne, NEJMed 2018*)
- Symptoms reduced; one study showed reduced exercise-induced bronchoconstriction

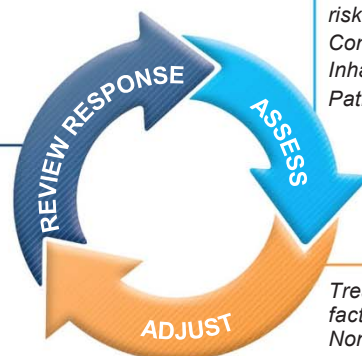
■ Values and preferences

- High importance was given to preventing severe exacerbations, avoiding need for daily ICS in patients with mild or infrequent symptoms, and safety of as-needed ICS-formoterol in maintenance and reliever therapy, with no new safety signals
- Lower importance given to small non-cumulative differences in symptom control (ACQ-5 difference 0.15 vs MCID 0.5) and lung function compared with daily ICS
- Makes use of normal patient behavior (seeking symptom relief) to deliver controller



Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



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Comorbidities
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Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications

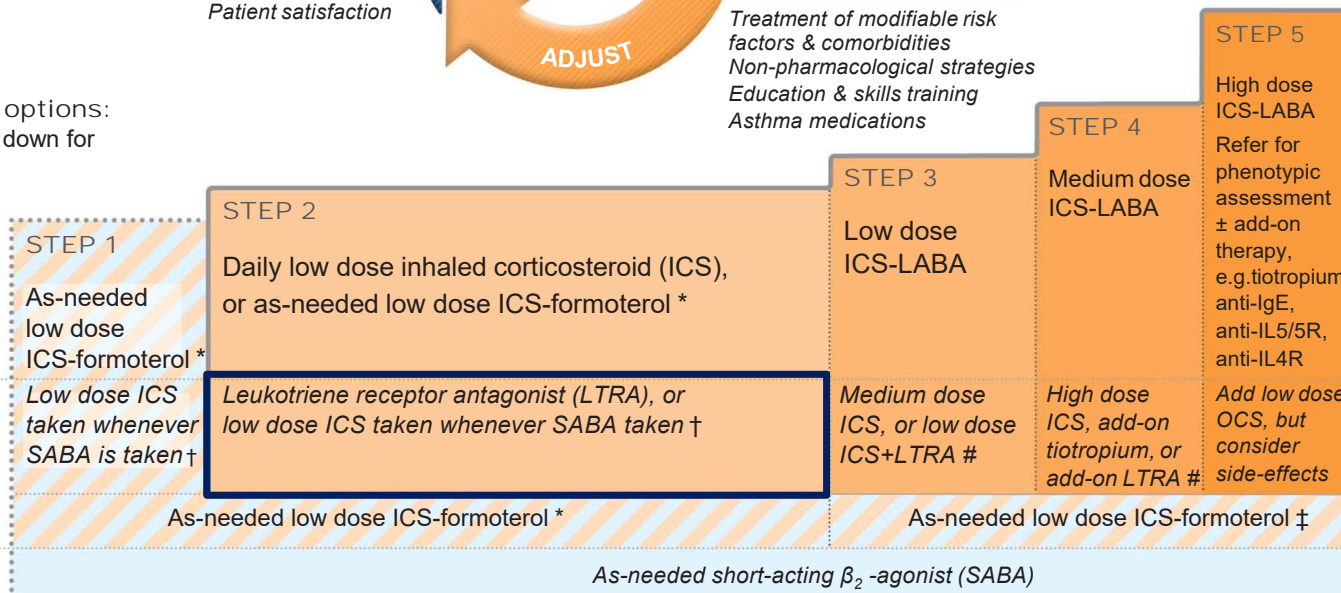
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PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER

Other reliever option



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‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy
Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted

Step 2 - other controller options



Low dose ICS taken whenever SABA taken (off-label, separate or combination inhalers)

■ Evidence

- Two RCTs showed reduced exacerbations compared with SABA-only treatment
 - BEST, in adults, with combination ICS-SABA (*Papi, NEJMed 2007*)
 - TREXA, in children/adolescents, with separate inhalers (*Martinez, Lancet 2011*)
- Three RCTs showed similar or fewer exacerbations compared with maintenance ICS
 - TREXA, BEST
 - BASALT in adults, separate inhalers, vs physician-adjusted treatment (*Calhoun, JAMA 2012*)

■ Values and preferences

- High importance given to preventing severe exacerbations
 - Lower importance given to small differences in symptom control and the inconvenience of needing to carry two inhalers
 - Combination ICS-SABA inhalers are available in some countries, but approved only for maintenance use
- Another option: leukotriene receptor antagonist (less effective for exacerbations)

Step 1 – rationale for changes in GINA 2019



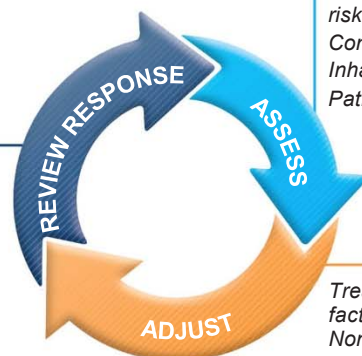
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Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



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Patient goals

Symptoms
Exacerbations
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Lung function
Patient satisfaction

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Non-pharmacological strategies
Education & skills training
Asthma medications

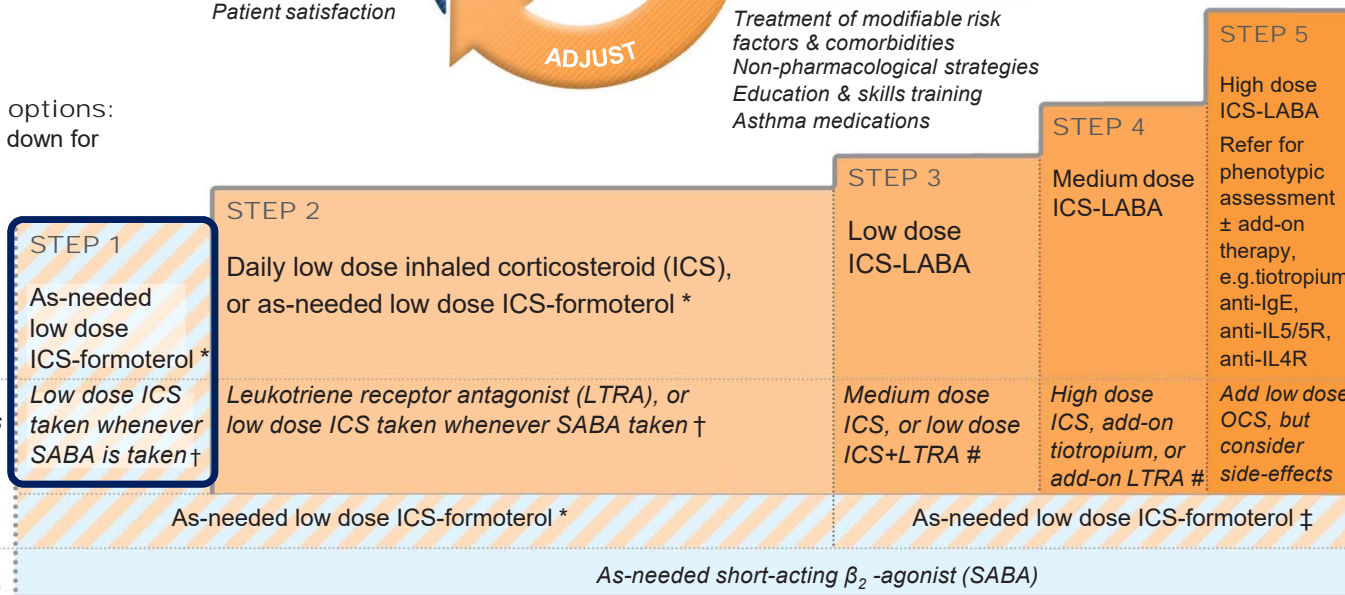
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Other reliever option



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Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV₁ >70% predicted



Step 1 – ‘preferred’ controller option

- Step 1 is for patients with symptoms less than twice a month, and with no exacerbation risk factors

As-needed low dose ICS-formoterol (off-label)

- Evidence
 - Indirect evidence from SYGMA 1 of large reduction in severe exacerbations vs SABA-only treatment in patients eligible for Step 2 therapy (*O’Byrne, NEJMed 2018*)
- Values and preferences
 - High importance given to reducing exacerbations
 - High importance given to avoiding conflicting messages about goals of asthma treatment between Step 1 and Step 2
 - High importance given to poor adherence with regular ICS in patients with infrequent symptoms, which would expose them to risks of SABA-only treatment



Step 1 - other controller option

Low dose ICS taken whenever SABA is taken (off-label)

- Evidence
 - Indirect evidence from studies in patients eligible for Step 2 treatment (BEST, TREXA, BASALT)
- Values and preferences
 - High importance given to preventing severe exacerbations
 - Lower importance given to small differences in symptom control and the inconvenience of needing to carry two inhalers
 - Combination ICS-SABA inhalers are available in some countries, but approved only for maintenance use

Daily ICS is no longer listed as a Step 1 option

- This was included in GINA 2014-18, but with high probability of poor adherence
- Now replaced by more feasible as-needed controller options for Step 1

Other changes in GINA 2019 - Steps 3-5 for adults and adolescents



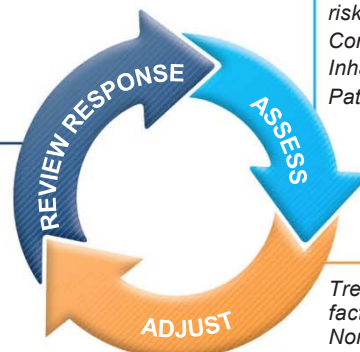
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Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



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Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Step 4 treatment is medium dose ICS-LABA; high dose now in Step 5

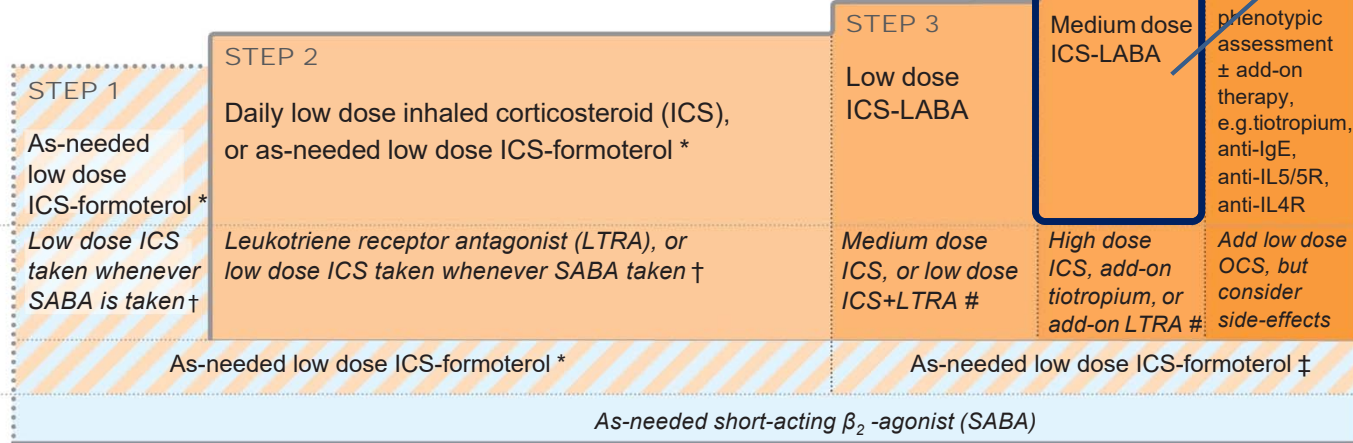
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Other controller options

PREFERRED RELIEVER

Other reliever option



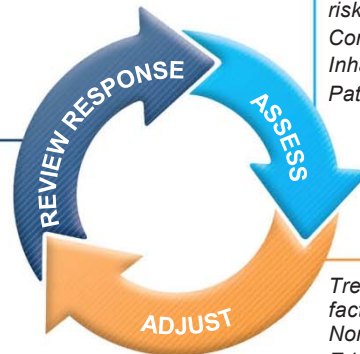
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Box 3-5A
Adults & adolescents 12+ years



Personalized asthma management:
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

See severe asthma Pocket Guide for details about Step 5

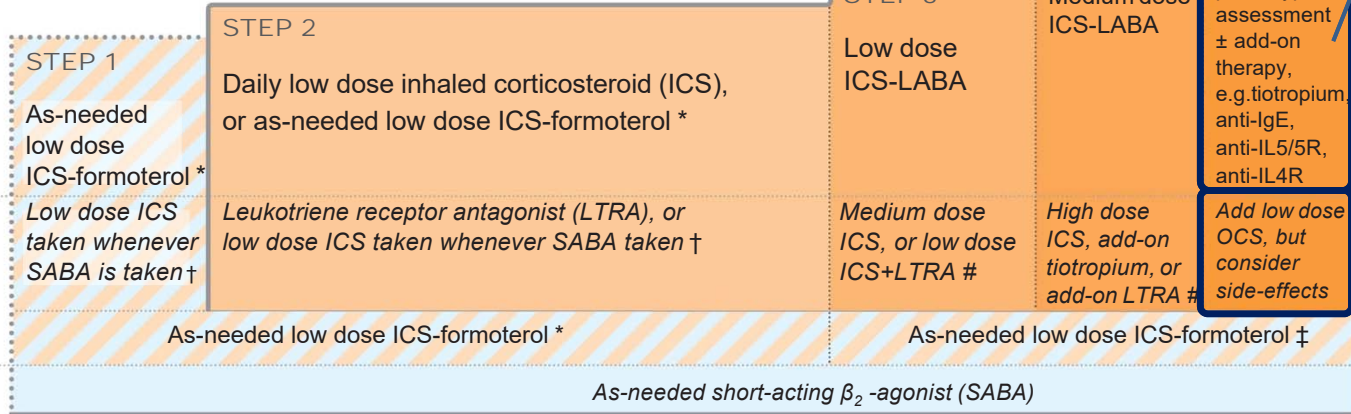
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Other controller options

PREFERRED RELIEVER

Other reliever option



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Changes in GINA 2019 – children 6-11 years



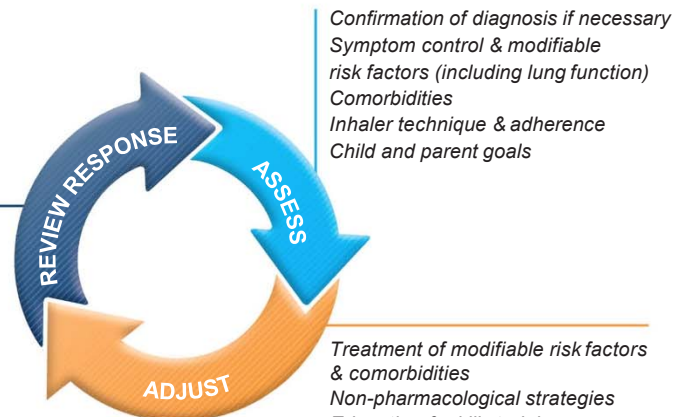
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Box 3-5B
Children 6-11 years



Personalized asthma management:
Assess, Adjust, Review response



Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Asthma medication options:
Adjust treatment up and down for individual child's needs

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

RELIEVER

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, or medium dose ICS	Medium dose ICS-LABA Refer for expert advice	Refer for phenotypic assessment ± add-on therapy, e.g. anti-IgE
	Low dose ICS taken whenever SABA taken*; or daily low dose ICS	Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	Low dose ICS+LTRA	High dose ICS-LABA, or add-on tiotropium, or add-on LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side-effects
	As-needed short-acting β_2 -agonist (SABA)				

* Off-label; separate ICS and SABA inhalers; only one study in children



Children 6-11 years

- Step 4
 - Medium dose ICS-LABA, but refer for expert advice
- Step 3
 - Low dose ICS-LABA and medium dose ICS are 'preferred' controller treatments
 - No safety signal with ICS-LABA in children 4-11 years (*Stempel, NEJMed 2017*)
- Step 2
 - Preferred controller is daily low dose ICS
 - Other controller options include as-needed low dose ICS taken whenever SABA is taken, but only one study in children (*Martinez, Lancet 2011*)
 - Studies of as-needed ICS-formoterol are needed; maintenance and reliever therapy with low dose budesonide-formoterol in children 4-11 years reduced exacerbations by 70-79% compared with ICS and ICS-LABA (*Bisgaard, Chest 2006*)
- Step 1
 - Low dose ICS whenever SABA taken (indirect evidence), or daily low dose ICS

Other changes in GINA 2019



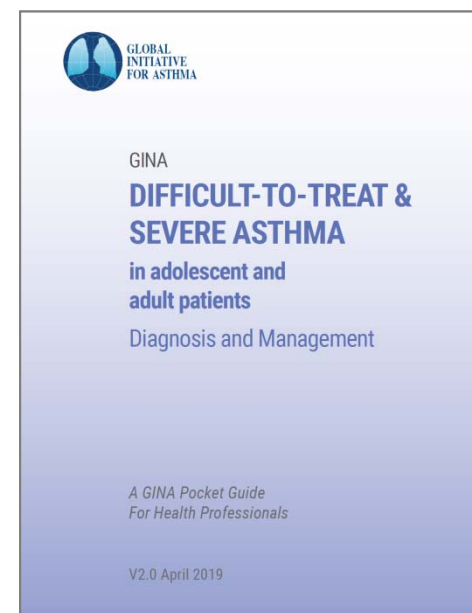
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Other changes in GINA 2019 – severe asthma

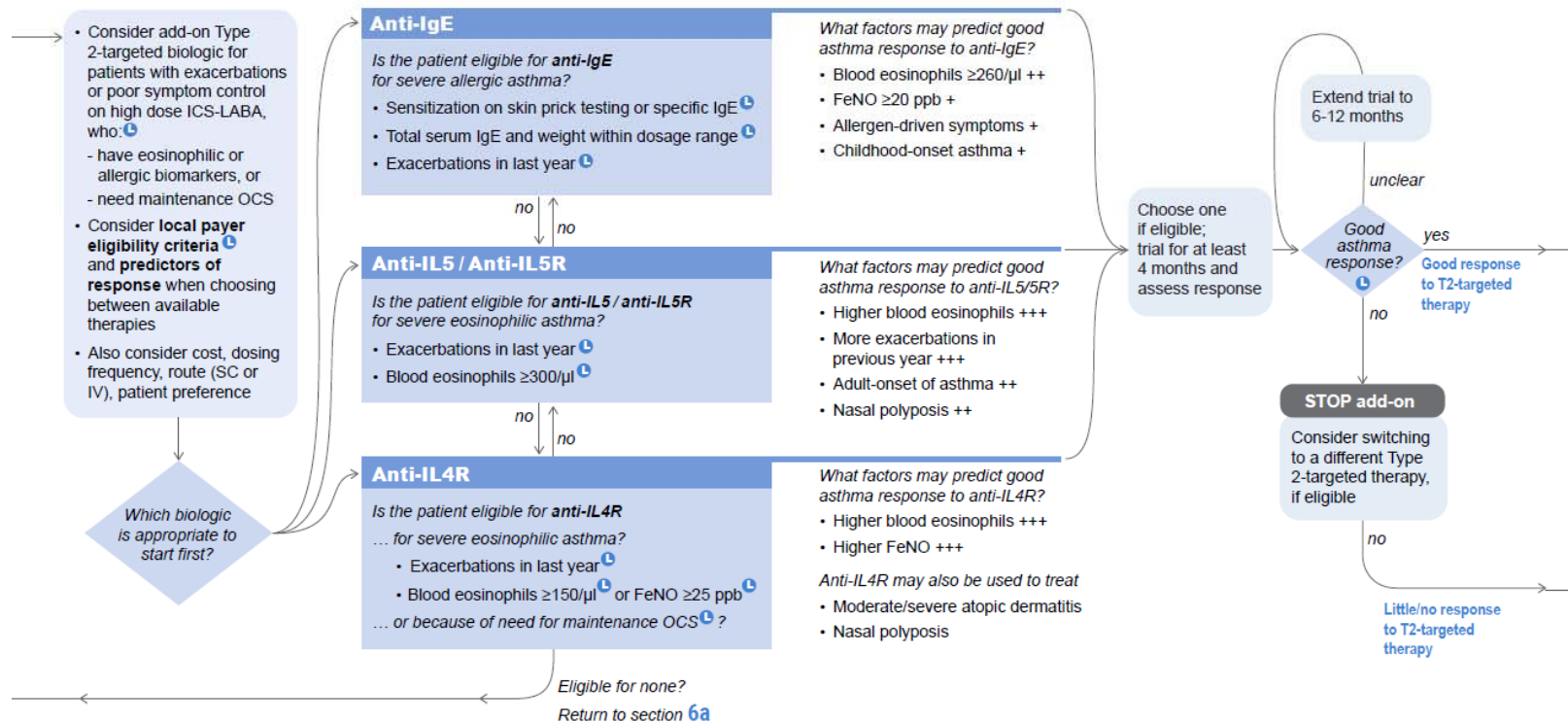
- **Pocket guide about difficult-to-treat and severe asthma**
 - A practical guide for primary and specialist care
 - Includes a decision tree about assessment and management of adults and adolescents with uncontrolled asthma or exacerbations despite Step 4-5 treatment
 - Includes strategies for clinical settings in which biologic therapy is not available or affordable
 - First published in November 2018
- **V2.0 Pocket Guide published April 2018**
 - Also included in full GINA 2019 report
 - Includes anti-IL4 receptor alpha (dupilumab)
 - Extension of biologic treatment trial to 6-12 months if response to initial therapy is unclear



Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments





Other changes in GINA 2019

- Updated strategies for 'yellow zone' of action plans, with new evidence
 - 4x increase in ICS dose decreased severe exacerbations in pragmatic study in adults (*McKeever, NEJMed 2018*)
 - 5x increase in ICS dose did not decrease severe exacerbations in children with good symptom control and high adherence (*Jackson, NEJMed 2018*)
- Pre-school asthma
 - Additional suggestions for investigating history of wheezing episodes
 - Early referral recommended if child fails to respond to controller treatment
 - For exacerbations, OCS not generally recommended except in ED setting
 - Follow-up after ED or hospital: within 1-2 working days and 3-4 weeks later
 - Pocket guide on management of asthma in children 5 years and younger will be updated in 2019

Questions?



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