

Online Repository

Appendixes.

Appendix E1. This systematic review has been conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (4), employing PubMed, EMBASE, and Global Health databases. On these websites, we searched for articles from January 1st, 2009, to October 2019, using key terms related to asthma attacks in pediatric population.

1. Asthma
2. Acute asthma
3. Exacerbation
4. Attack
5. Flare up
6. Child
7. Children
8. Adolescent
9. 1 or 2 or 3 or 4 or 5
10. 6 and 7 and 8
11. Guideline/ or practice guideline/
12. Guidelines as topic/ or practice guidelines as topic/
13. (guideline* or algorithm* or standard*).ti.ab.
14. “best practice”.ti.ab.
15. 11 or 12 or 14

Appendix E2. AGREE II instrument domains

Domain 1 – Scope and Purpose

- The overall objective(s) of the guideline is (are) specifically described
- The health question(s) covered by the guideline is (are) specifically described
- The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described

Domain 2 – Stakeholder Involvement

- The guideline development group includes individuals from all relevant professional groups
- The views and preferences of the target population (patients, public, etc.) have been sought
- The target users of the guideline are clearly defined

Domain 3 – Rigor of Development

- Systematic methods were used to search for evidence
- The criteria for selecting the evidence are clearly described
- The strengths and limitations of the body of evidence are clearly described
- The methods for formulating the recommendations are clearly described
- The health benefits, side effects and risks have been considered in formulating the recommendations
- There is an explicit link between the recommendations and the supporting evidence
- The guidance has been externally reviewed by experts prior to its publication
- A procedure for updating the guideline is provided

Domain 4 – Clarity of Presentation

- The recommendations are specific and unambiguous
- The different options for management of the condition or health issue are clearly presented

- Key recommendations are easily identifiable

Domain 5 – Applicability

- The guideline describes facilitators and barriers to its application
- The guideline provides advice and/or tools on how the recommendations can be put into practice
- The potential resource implications of applying the recommendations have been considered
- The guideline presents monitoring and/or auditing criteria

Domain 6 – Editorial Independence

- The views of the funding body have not influence the content of the guideline
- Competing interests of guideline development group members have been recorded and addressed

Table E1. Definition of severity asthma exacerbation.

Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)	German GL (2017)
Not stated	<i>Mild</i> In accordance with clinical and objective assessment	<i>Mild</i> Not specified	<i>Mild</i> It's just outside the normal range of variation for an individual patient	Not stated	<i>Non-severe</i> Not fulfilling the criteria for severe or life-threatening asthma	<i>Mild</i> Not specified	<i>Mild</i> In accordance to clinical and objective assessment	<i>Mild</i> Defined as good asthma control achievable with medication of therapy level 1 (low ICS* dose) or level 2 (low ICS dose plus anti-LT)
	<i>Moderate</i> In accordance with clinical and objective assessment	<i>Moderate</i> Not specified	<i>Moderate</i> Defined as at least one of the following occurring for at least two days without the need for systemic CS*: increasing asthma symptoms, worsening lung function, and/or increased rescue bronchodilator use.		<i>Severe</i> Presence of two or more of the following: inability to complete sentences, agitation, use of accessory muscles, respiratory rate >30/minute more of the following) heart rate >110/minute, pulsus paradox >25mmHg, silent chest, PEF* <60% of predicted or personal best, PaO ₂ * <60 mmHg or SpO ₂ * <92%	<i>Moderate</i> Not specified	<i>Moderate</i> In accordance to clinical and objective assessment	<i>Moderate</i> Defined as good asthma control achievable with medication of therapy level 3 (medium ICS dose) or level 4 (medium ICS dose plus LABA* plus SABA* or high ICS dose plus LABA plus SABA)
	<i>Severe</i> In accordance with clinical and objective assessment	<i>Severe</i> Not specified	<i>Severe</i> Defined as either an asthma related hospitalization or a visit to the ED* or an urgent care facility, together with treatment with systemic CS for at least three days		<i>Life-threatening</i> Any feature	<i>Severe</i> Not specified	<i>Severe</i> In accordance to clinical and objective assessment	<i>Severe</i> Not well-controlled asthma under high-dose ICS-LABA therapy or loss of asthma control when reducing this high dose ICS-LABA therapy; need of therapy level 5 (biologic drugs)
		<i>Very severe</i> Not specified	<i>Acute severe</i> Severe asthma unresponsive to			<i>Respiratory failure</i>		

			repeated courses of β 2-agonist therapy			Not specified		
			<i>Near-fatal</i> Acute severe asthma associated with a respiratory arrest or hypercarbia					

Continued

Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
<i>Mild</i> In accordance with clinical and objective assessment	<i>Mild</i> In accordance to clinical and objective assessment	Not stated	<i>Mild</i> Not specified	<i>Mild</i> In accordance to clinical and objective assessment	Not stated	<i>Moderate</i> In accordance to clinical and objective assessment
<i>Moderate</i> In accordance with clinical and objective assessment	<i>Moderate</i> In accordance to clinical and objective assessment		<i>Moderate</i> Not specified	<i>Moderate</i> In accordance to clinical and objective assessment		<i>Severe</i> In accordance to clinical and objective assessment
<i>Severe</i> In accordance with clinical and objective assessment	<i>Severe</i> In accordance to clinical and objective assessment		<i>Severe</i> Not specified	<i>Severe</i> In accordance to clinical and objective assessment		<i>Life-threatening</i> In accordance to clinical and objective assessment
			<i>Life-threatening</i> Not specified	<i>Life-threatening</i> In accordance to clinical and objective assessment		

*CS: corticosteroid; ED: emergency department; ICS: inhaled corticosteroid; LABA: long-acting beta-agonists; SABA: short-acting beta-agonists; anti-LT: anti-leukotrienes; PEF: Peak expiratory flow; PaO₂: Partial Pressure of Oxygen; SpO₂: Oxygen saturation.

	Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Poor inhaler technique	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Underuse or poor adherence to treatment	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Discontinuous medical care	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Socioeconomic disadvantage	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Obesity	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Alternative therapies	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Hypoxemia at initial management	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Sputum or blood eosinophilia	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Psychological factors	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated

Continued

	German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
Allergen exposure	Yes	Yes	Not stated	Yes	Yes	Yes	Yes	Yes
Environmental tobacco	Yes	Yes	Not stated	Yes	Yes	Yes	Yes	Yes
Air pollution	Yes	Yes	Not stated	Yes	Yes	Not stated	Not stated	Yes
Diet	Yes	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated
No Vaccination	Yes	No	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Comorbidities	Yes	Yes	Not stated	Yes	Yes	Yes	Not stated	Not stated

Cold air	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Extreme emotional arousal	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Physical exercise	Yes	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
Aspirin and other nonsteroidal anti-inflammatory drugs	Yes	Yes	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
Beta-blockers	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Poor asthma control	Yes	Yes	Not stated	Not stated	Not stated	Yes	Yes	Not stated
Hospitalization or emergency department visit for asthma in the last year	Yes	Not stated	Not stated	Yes	Not stated	Not stated	Yes	Not stated
Extreme inhaled bronchodilator use	Yes	Yes	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Intensive care admission or intubation	Yes	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Requirement for long-term oral CS	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Poor inhaler technique	Yes	Not stated	Not stated		Not stated	Yes	Not stated	Not stated
Underuse or poor adherence to treatment	Yes	Not stated	Not stated	Yes	Not stated	Yes	Not stated	Not stated
Discontinuous medical care		Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Socioeconomic disadvantage	Not stated	Yes	Not stated	Not stated	Yes	Yes	Not stated	Not stated
Obesity	Yes	Not stated	Not stated	Not stated	Yes	Yes	Yes	Not stated
Alternative therapies	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated
Hypoxemia at initial management	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated
Sputum or blood	Yes	Yes	Not stated	Yes	Not stated	Not stated	Not stated	Not stated

eosinophilia								
Psychological factors	Yes	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

*GL: guideline; CS: corticosteroid.

Table E3. Assessment of asthma exacerbation.

	Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)
<i>Clinical signs</i>							
Pulse rate	Not stated	Yes	Not stated	Yes	Yes	Not stated	Yes
Respiratory rate and degree of breathlessness	Not stated	Yes	Not stated	Yes	Yes	Not stated	Yes
Use of accessory muscles of respiration/Dyspnea	Not stated	Yes	Not stated	Yes	Yes	Not stated	Yes
Amount of wheezing	Not stated	Yes	Not stated	Yes	Yes	Not stated	Yes
Degree of agitation and level of consciousness	Not stated	Not stated	Not stated	Yes	Yes	Not stated	Yes
Heart Rate	Not stated	Yes	Not stated	Yes	Yes	Not stated	Not stated
<i>Investigations</i>							
Pulse oximetry	Not stated	Yes	Not stated	SpO ₂ <92	SpO ₂ <90	SpO ₂ <92	Yes
PaCO₂*	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
PEF*	Not stated	Not stated	Not stated	Not stated	<50% of predicted or best	<60% of predicted or best	Yes
Chest X-ray	Not stated	Not stated	Not stated	No	Not stated	Yes, if clinically indicated	Not stated
Arterial blood gas	Not stated	Not stated	Not stated	Yes	Not stated	Yes if SpO ₂ <92 or PEF does not improve to 40% to 45% of predicted or personal best or who worsen during or after treatment.	Yes
Electrocardiogram and/or echocardiogram	Not stated	Not stated	Not stated	Not stated	Not stated	Yes, if clinically indicated	Not stated
Blood examinations	Not stated	Not stated	Not stated	Not stated	Not stated	Yes, if clinically indicated	Not stated

Continued

	New Zealand GL (2017)	German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
<i>Clinical signs</i>									
Pulse rate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Respiratory rate and degree of breathlessness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Use of accessory muscles of respiration/Dyspnea	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Amount of wheezing	Not stated	Not stated	Yes	Yes	Yes	Yes	Not stated	No	Yes
Degree of agitation and level of consciousness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Heart Rate	Not stated	Yes	Yes	Yes	Yes	Yes	Not stated	No	Yes
<i>Investigations</i>									
Pulse oximetry	Not stated	Yes	Yes	Yes	SpO ₂ <92	Yes	Yes	Not stated	SpO ₂ <92
PaCO₂	Not stated	Yes	Yes	Yes	Not stated	Not stated	Not stated	Yes	No
PEF	Not stated	Yes	Yes	Yes	< 50% predicted	< 50% predicted	Yes	Not stated	No
Chest X-ray	Not stated	Not stated	Not stated	Not stated	Yes, if complications	Yes, if complications	Not stated	Yes, if complications	No
Arterial blood gas	Not stated	Yes	Not stated	Not stated	Not stated	Yes, if complications	Not stated	Yes, for severe exacerbation or exacerbations that fail to	Yes, if complications

								respond to initial treatment	
Electrocardiogram and/or echocardiogram	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Blood examinations	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

*GL: guideline; PaCO₂: partial pressure of carbon dioxide; PEF: Peak expiratory flow.

Table E4. Treatment of asthma exacerbation in accordance with severity disease.

Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Salbutamol Recommended	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>
Terbutaline Recommended	Salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended
Formoterol Recommended, only in children older than 12 yrs*		Inhaled ipatropium bromide Recommended	Inhaled formoterol Recommended	Oral prednisone Recommended	<i>Moderate</i>	Inhaled formoterol Not Recommended	Inhaled procaterol Recommended
Hydrocortisone Not stated	<i>Moderate</i>	<i>Moderate</i>	ICS* Not Recommended	<i>Moderate</i>	Inhaled salbutamol Recommended	ICS Not Recommended	Inhaled disodium cromoglycate Recommended
Prednisolone Recommended	Oxygen supplementation: (SpO ₂ * <92%) Recommended	Oxygen supplementation: (SpO ₂ * >95%) Recommended	<i>Moderate</i>	Inhaled salbutamol Recommended	Oral prednisolone Recommended	Oral prednisone Recommended if there is no response to salbutamol in one hour	<i>Moderate</i>
Budesonide Recommended	Inhaled Salbutamol Recommended	Oral prednisolone Recommended	Oxygen supplementation: (SpO ₂ <95%) Recommended	Oral prednisone Recommended	<i>Severe</i>	<i>Moderate</i>	Inhaled salbutamol Recommended
			Oral prednisolone Recommended		Oxygen supplementation: (SpO ₂ >93%) Recommended	Inhaled salbutamol Recommended	Oxygen supplementation: (SpO ₂ <95%) Recommended
						Oral prednisolone	

Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Inhaled ipratropium bromide Recommended, as second-line reliever in severe exacerbation Theophylline Not stated	Salbutamol+ ipratropium bromide Recommended IV CS (Hydrocortisone, Methylprednisolone or Prednisone) Recommended		Recommended Methylprednisolone Recommended Dexamethasone Recommended			Recommended	IV CS (Hydrocortisone, Prednisolone, Methylprednisolone, Betamethasone or dexamethasone) Recommended Aminophylline Recommended with caution
Aminophylline Not stated	<i>Severe</i> Oxygen supplementation: (SpO ₂ * <92%) Recommended Inhaled salbutamol Recommended Salbutamol+ ipratropium bromide Recommended IV CS (hydrocortisone, methylprednisolone or prednisone) Recommended IV salbutamol Consider IV magnesium sulphate Consider	<i>Severe</i> IV β-2 agonists Recommended IV aminophylline Recommended IV magnesium sulfate Recommended Helium–oxygen mixture Recommended	<i>Severe</i> IV β-2 agonists Recommended Theophylline Recommended IV aminophylline, Recommended IV magnesium sulfate Recommended Helium–oxygen mixture Recommended Intravenous fluids Not Recommended Adrenaline Recommended, in an	<i>Severe</i> Inhaled salbutamol+ Oxygen supplementation Recommended Oral prednisone Recommended Inhaled ipratropium bromide Recommended IV hydrocortisone Recommended		<i>Severe</i> Oxygen supplementation Oxygen should be used only in hypoxaemic patients Salbutamol+ ipratropium bromide Recommended IV β2-agonists and theophylline Recommended if inhaled medications are ineffective Systemic CS (prednisolone, dexamethasone, methylprednisolone, prednisolone, hydrocortisone) Recommended IV or inhaled magnesium sulphate	<i>Severe</i> Inhaled salbutamol + oxygen supplementation Recommended IV CS (hydrocortisone, prednisolone, methylprednisolone, betamethasone or dexamethasone) Recommended Inhaled isoproterenol Recommended with caution

Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
			<p>emergency situation where inhaled therapy is not available</p> <p>Antibiotics Not Recommended</p>			<p>Recommended if severe asthma not responding to a combination of inhaled β2-agonist, anticholinergic and systemic CS</p> <p>NIV* Recommended but it should be judiciously used</p> <p>Heliox Recommended but it should be not routinely used</p>	

Continued

German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>	<i>Mild</i>
Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Not stated	Not stated
Oral prednisolone Recommended		Oral CS Recommended	Inhaled ICS Recommended	Inhaled ipratropium bromide Recommended	Oral prednisone Recommended	Moderate	Moderate
			Oral prednisolone Recommended	Oral prednisolone Recommended	Oxygen supplementation (SpO ₂ <94%) Recommended	Not stated	Inhaled salbutamol Recommended
<i>Moderate</i>	<i>Moderate</i>	<i>Moderate</i>		Oral leukotriene receptor antagonists Recommended	Moderate	Continuous nebulization β2-agonists Recommended	Oxygen supplementation (SpO ₂ <92%) Recommended
Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled salbutamol Recommended	Inhaled ipratropium bromide Recommended		Inhaled salbutamol Recommended	Inhaled ipratropium bromide Recommended	Oral prednisolone Recommended
Oral prednisone Recommended	Oral prednisone Recommended	Inhaled ipratropium bromide Recommended	<i>Moderate</i>		Oral prednisone Recommended	IV or orally methylprednisolone or hydrocortisone Recommended	<i>Severe</i>
<i>Severe</i>	<i>Severe</i>	Oral CS Recommended	Inhaled salbutamol Recommended	Inhaled magnesium sulphate Not Recommended	Oxygen supplementation (SpO ₂ <94%) Recommended	IV magnesium sulfate Recommended	Inhaled ipratropium bromide Recommended
Inhaled salbutamol+ Oxygen supplementation Recommended			Inhaled CS Recommended	IV aminophylline Not Recommended	Severe	Oxygen supplementation (SpO ₂ <94%) Recommended	IV magnesium sulfate Recommended
Oral prednisone Recommended	Oxygen supplementation (SpO ₂ <94%) Recommended	<i>Severe</i>	Oral prednisolone Recommended	<i>Moderate</i>	Inhaled salbutamol Recommended	Antibiotics Recommended for complications	<i>Life-threatening asthma</i>
Inhaled Ipratropium bromide Recommended	Inhaled salbutamol Recommended	Oxygen supplementation (SpO ₂ <95%) Recommended	Inhaled ipratropium bromide Recommended	Inhaled magnesium sulphate Not Recommended	Inhaled	NIV Recommended when	Inhaled salbutamol + ipratropium bromide Recommended
		Inhaled salbutamol		IV aminophylline Not Recommended			IV methylprednisolone or

<p>IV prednisone Recommended</p> <p>IV magnesium sulphate Recommended</p> <p>IV Terbutalin Recommended</p> <p>IV Reproterol Recommended</p> <p>IV bicarbonate in case of acidosis (pH<7.2)</p>	<p>Inhaled ipratropium bromide Recommended</p> <p>Oral prednisone Recommended</p>	<p>Recommended</p> <p>Inhaled ipratropium bromide Recommended</p> <p>Oral CS Recommended</p> <p>IV magnesium sulphate Recommended</p> <p>IV salbutamol Recommended</p> <p>IV aminophylline Recommended</p>	<p><i>Severe</i></p> <p>Oxygen supplementation (SpO₂ <93%) Recommended</p> <p>Oral prednisolone or IV methylprednisolone Recommended</p> <p>IV magnesium sulphate Recommended</p> <p>NIV No specific recommendations</p> <p>Antibiotics Not Recommended</p>	<p><i>Severe</i></p> <p>IV salbutamol Recommended</p> <p>Inhaled Ipratropium bromide Recommended</p> <p>Oxygen supplementation (SpO₂ <94%) Recommended</p> <p>IV hydrocortisone Recommended</p> <p>Inhaled magnesium sulphate Recommended</p> <p>Oral leukotriene receptor antagonists Not Recommended</p> <p>Antibiotics Not Recommended</p> <p>IV aminophylline Recommended when asthma unresponsive to maximal doses of bronchodilators and CS</p> <p>Other therapies (Heliox, ketamine,</p>	<p>ipratropium bromide Recommended</p> <p>Oral CS Recommended</p> <p>Oxygen supplementation Recommended</p>	<p>conventional treatments fail</p> <p>High-flow nasal oxygen Not Recommended</p> <p>Ketamine and halogenated Not Recommended</p> <p>Helium Not Recommended</p> <p>ECMO* Recommended in the case of respiratory acidosis and/or severe hypoxemia refractory to optimal medical treatment and to well-conducted mechanical ventilation</p>	<p>IV hydrocortisone Recommended</p>
---	---	--	---	---	---	---	--

				sevoflurane, ECMO, recombinant human deoxyribonuclease, NIV) Not Recommended			
--	--	--	--	--	--	--	--

*GL: guideline; CS: corticosteroid; ICS: inhaled corticosteroid; SpO2: Oxygen saturation; IV: intravenous; NIV: non invasive ventilation; ECMO: extracorporeal membrane oxygenation

Table E5. Drug dosage according to each included guideline

	Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Inhaled β2-agonists	Not stated	Salbutamol from 2 to 4 puffs (200–1000 lg), every 20 minutes for the first three hours OR Salbutamol 2 puffs (200–1000 lg), every 10 minutes for the first three hours given via MDI*-spacer (nebulized also possible).	Salbutamol from 2 to 10 puffs (200–1000 lg), every 20 min for the first hour, given via MDI*-spacer (nebulized also possible). IB*, 2–8 puffs; or nebulized, 0.25–0.5 mg	Salbutamol 2 to 10 puffs every 20 minutes, given via MDI-spacer. Nebulised salbutamol 2.5 - 5 mg or 0.5-1 mg fenoterol + saline to make nebuliser volume up to 4 ml IB 250 μ g/dose to 2.5-5.0 mg of salbutamol or 0.5-1mg fenoterol, every 20-30 minutes initially then 4-6h	Not stated	Salbutamol: 4-6 puffs of 100 μ g salbutamol every 30 Minutes Continuous nebulisation: 2.5 mg every 15 minutes, or >4 nebulisation/h Intermittent nebulisation: 2.5 mg every 20 minutes, or <3 nebulisation/ The subsequent dose should be 2.5 mg every 2-4h IB: 500 μ g once, then 250 μ g q4-6 h	Salbutamol or Procaterol: 0.1-0.3 mL to infants or 0.3-0.5 mL to school children or adolescents Disodium cromoglycate inhalant solution: 1 ampule = 2 mL	Salbutamol: 6 x 100 μ g via MDI and spacer or 2.5-5.0 mg via nebulization up to 3 times over 1 st hour IB: 4 x 200 μ g via MDI and spacer or 2.5 mg via nebulization
IV* β2-agonists	Not stated	Salbutamol: Bolus dose only: 15 μ g/kg over 10 minutes Continuous infusion: load 1-2 μ g/kg/min of 200 ug/ml solution	Not stated	Salbutamol: Bolus dose only: 15 μ g/kg over 10 minutes Continuous infusion: load 5-10 μ g/kg/min of 1 mg/ml solution at 0.3 - 0.6 ml/kg/h for 1 hour, then salbutamol infusion 1-5 μ g/kg/min of a 1mg/ml solution at 0.06 -0.3 ml/kg/h	Not stated	Not stated	Not stated	Not stated
Inhaled CS*	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Oral CS	Prednisone 1- 2 mg/kg for 3-5 days	Prednisone 1 mg/kg	Prednisolone 1–2mg/kg/24h for 3–5 days	Prednisone or prednisolone 1-2 mg/kg (Recommended dose 20 mg for children aged 2-5 yrs and 30-40 mg	Prednisolone 1 mg/kg, maximum 50 mg/24h	Prednisone 30-40 mg/day for 5-7 days	Prednisolone 0.5-1.0 mg/kg/day	Prednisone 1–2 mg/kg (to a maximum of 40 mgs)/24h for 3–5

Continued

	German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
Inhaled β2-agonists	<p>Salbutamol</p> <p>2 to 4 puffs every 10-15 minutes, given via MDI-spacer.</p> <p>10-20 drops in 1ml NaCl via nebulization every 20 minutes</p> <p>IB:</p> <p>0.5 mg via nebulization</p> <p>80 µg via MDI and spacer</p>	<p>Salbutamol</p> <p>2 to 10 puffs every 20 minutes, given via MDI-spacer.</p> <p>0,15 mg x kg (max 5 mg) via nebulization every 20 minutes up to 3 times</p> <p>IB:</p> <p>250 µg <30Kg or 500 µg >30Kg via nebulization</p> <p>40-80 µg via MDI and spacer</p>	<p>Salbutamol:</p> <p>200–400 µg/dose (2–4 puffs/dose up to 3 times every 20–30 min within the first hour, via MDI with spacer</p> <p>2.5 to 5 mg via nebulization</p> <p>IB:</p> <p>125–250 µg/dose (in children < 4 years of age) to 250–500 µg/dose (in children ≥ 4 years of age), in combination with nebulized salbutamol. It should be administered frequently, up to 3 times every 20–30 min, within the 1st h</p>	<p>Salbutamol:</p> <p>4–10 puffs every 20 min for the first hour via MDI with spacer</p>	<p>Salbutamol:</p> <p>via nebulizer (preferably oxygen-driven), 2.5 to 5 mg or, if nebuliser not available via spacer</p> <p>IB:</p> <p>0.25 mg every 20 minutes for 1–2h</p>	<p>Salbutamol:</p> <p>4–10 puffs every 20 min for the first hour via MDI with spacer</p>	<p>IB:</p> <p>0.5mg dose every 8 h in children over 6 years of age, and a 0.25-mg dose every 8 h in children under 6 years of age</p>	<p>Salbutamol:</p> <p>4–10 puffs every 20 min for 1 h, then every 1–2 h according to response</p> <p>2.5–5 mg every 20 min for 1 h, then every 2 h according to response (driven by oxygen if patient is hypoxic) via nebulization</p> <p>IB:</p> <p>4–8 puffs every 20 min and then every 4–6 h as needed via MDI with spacer</p> <p>0.5 mg every 20 min for 3 doses by the nebulized route and then every 4–6 h as needed via nebulization</p> <p>Salbutamol + IB: salbutamol at 10–15 mg with IB at 1.5 mg over 1 h</p>
IV* or SC* β2-agonists	<p>Terbutaline:</p> <p>0.25-0.5mg sc over 4 hours</p> <p>Reproterol:</p>	<p>Not stated</p>	<p>Salbutamol:</p> <p>single bolus of 15 µg/kg over 10 min^{###}, followed by continuous infusion of 0.2 µg/kg /min. Higher doses (1–2</p>	<p>Not stated</p>	<p>Salbutamol:</p> <p>Bolus IV 15ug/kg</p> <p>Continuous infusion 1–5</p>	<p>Not stated</p>	<p>Not stated</p>	<p>Not stated</p>

	0.09 mg IV or 0.018-0.09 mg/hour		µg/kg/min up to 5 µg/kg/min) can be administered in unresponsive children		ug/kg/min (200 ug/ml solution)			
Inhaled CS*	Not stated	Not stated	ICS should not be used	Not stated	Not stated	Not stated	Not stated	Not stated
Oral CS	Prednisone 1–2 mg/kg every 4-6 hours	Prednisone 1–2 mg/kg (to a maximum of 40 mg)/24h for 3–5 days	Prednisone or dexamethasone or prednisolone: single or 2-dose over 5-days	Prednisone: 40–50 mg/day for 5–7 days	Prednisone: 30–40 mg/day for 3–5 days	Prednisone 1–2 mg/kg (to a maximum of 40 mg)	Not stated	Prednisolone: 1 mg/kg/day to maximum of 50 mg
IV CS	Prednisone 1–2 mg/kg every 4-6 hours	Not stated	Prednisone or dexamethasone or prednisolone: single or 2-dose over 5-days	Methylprednisolone: Dosage not stated	Hydrocortisone 4 mg/kg	Not stated	Methylprednisolone: 2 mg/kg of maximum 80 mg per day	Hydrocortisone: 200 mg Methylprednisolone: 80 mg
Oxygen supplementation	Aims at SaO ₂ > 92%	Aims at SaO ₂ > 94%	Not stated	Aims at SaO ₂ > 93%	Aims at SaO ₂ > 94%	Aims at SaO ₂ > 94%	Aims at SaO ₂ > 94%	Aims at SaO ₂ > 92%
IV Aminophylline	Not stated	Not stated	Not stated	Not stated	5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1mg/kg/hour	Not stated	Not stated	1–2 g over 20 min
IV Magnesium sulphate	2g/20 minutes	Not stated	Not stated It should not be used	Not stated	40 mg/kg (max 2 g) over 20 minutes	Not stated	Not stated	Not stated
Inhaled Magnesium sulphate	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	dose ≥ 20 mg/kg	Not stated
IV Bicarbonates	Not specified	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Epinephrine	Not stated	Not stated	Not stated It could be used if β ₂ -agonists are not available	Not stated	Not stated	Not stated	Not stated	Not stated
Helium-oxygen	Not stated	Not stated	Not stated It could be used in severe asthma unresponsive to standard therapy	Not stated	Not stated	Not stated	Not stated	Not stated
NIV*	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	It should probably be considered when	Not stated

							conventional treatments fail	
--	--	--	--	--	--	--	------------------------------------	--

*MDI: Metered Dose Inhaler; IB: ipatropium bromure; IV: intravenous; SC: subcutaneous; SpO2: partial oxygen saturation.

The loading dose should be omitted in children receiving maintenance oral theophylline; ## dilution: 200 µg/mL for central iv line; 10–20 µg/mL for peripheral iv line

Table E6. Criteria hospitalization for asthma exacerbation.

	Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Silent Chest	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Cyanosis	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Poor respiratory effort	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Hypotension, bradycardia	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Exhaustion	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Confusion or drowsiness	Not stated	Yes	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Unable to complete sentences in one breath; too breathless to talk or feed	Not stated		Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Agitation	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Accessory muscle use	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Tachycardia	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Tachypnea	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
SpO₂* <92%	Not stated	Yes	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
PEF* <50% predicted	Not stated	Yes	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Moderately severe asthma not responding to β₂-agonist therapy	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Yes
Home circumstances which do not allow safe or reliable treatment	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Yes
Complications	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated
Severe exacerbation and respiratory failure	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Yes
Moderate exacerbation with past history of severe exacerbation or not improved by ambulatory treatment for about 2 hours	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated

Age	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated
Presentation at night	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
History of previous severe life-threatening asthma episodes	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated

Continued

	German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
Silent Chest	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Cyanosis	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Poor respiratory effort	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Hypotension, bradycardia	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Exhaustion	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Confusion or drowsiness	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Yes
Unable to complete sentences in one breath; too breathless to talk or feed	Not stated	Not stated	Not stated	Not stated	Not stated		Not stated	Yes
Agitation	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Accessory muscle use	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Tachycardia	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes
Tachypnea	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	
SpO₂ <92%	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Yes
PEF <50% predicted	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated
Moderately severe asthma not responding to β₂-agonist therapy	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Home circumstances which do not allow safe or reliable treatment	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
Complications	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated
Severe exacerbation	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated	Not stated

and respiratory failure								
Moderate exacerbation with past history of severe exacerbation or not improved by ambulatory treatment for about 2 hours	Not stated	Not stated	Yes	Not stated	Not stated	Yes	Not stated	Not stated
Age	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated
Presentation at night	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
History of previous severe life-threatening asthma episodes	Not stated	Not stated	Yes	Not stated	Not stated	Yes	Yes	Yes

GL: guideline; SpO₂: SpO₂: Oxygen saturation; PEF: Peak expiratory flow.

Table E7. Discharge criteria for asthma exacerbation.

	Canadian GL* (2010)	Latin America and Spain GL (2010)	ICON GL (2012)	South African GL (2013)	Korean Asthma GL (2014)	Indian GL (2015)	Japanese GL (2017)	New Zealand GL (2017)
Stable on 3 - 4-hourly inhaled bronchodilators that	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Normal breath rate	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
No chest wall indrawing	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
SpO₂* >94% in room air	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
PEF* and/or FEV1* should be >75% of best or predicted	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Not stated	Not stated
Appropriate care	Not stated	Not stated	Not stated	Yes	Yes	Not stated	Not stated	Yes

can be provided at home								
Written asthma action plan	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated	Yes
Stable for at least 24 hours	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated

Continued

	German GL (2017)	Spanish GL (2018)	Italian GL (2018)	Swiss GL (2018)	British and Scottish GL (2019)	GINA GL (2019)	French GL (2019)	Saudi Arabia GL (2019)
Stable on 3 - 4-hourly inhaled bronchodilators	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
Normal breath rate	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
No chest wall indrawing	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
SpO2 >94% in room air	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
PEF and/or FEV1 should be >75% of best or predicted	Not stated	Not stated	Not stated	Not stated	Not stated	Yes	Not stated	Not stated
Appropriate care can be provided at home	Not stated	Not stated	Not stated	Yes	Yes	Yes	Not stated	Yes
Written asthma action plan	Not stated	Not stated	Not stated	Yes	Yes	Yes	Not stated	Yes
Stable for at least 24 hours	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated

*GL: Guideline; SpO2: oxygen saturation; PEF: peak expiration flow; FEV1: Forced expiratory volume in 1 second.