Acute infection exacerbation of chronic lung Disease - asthma

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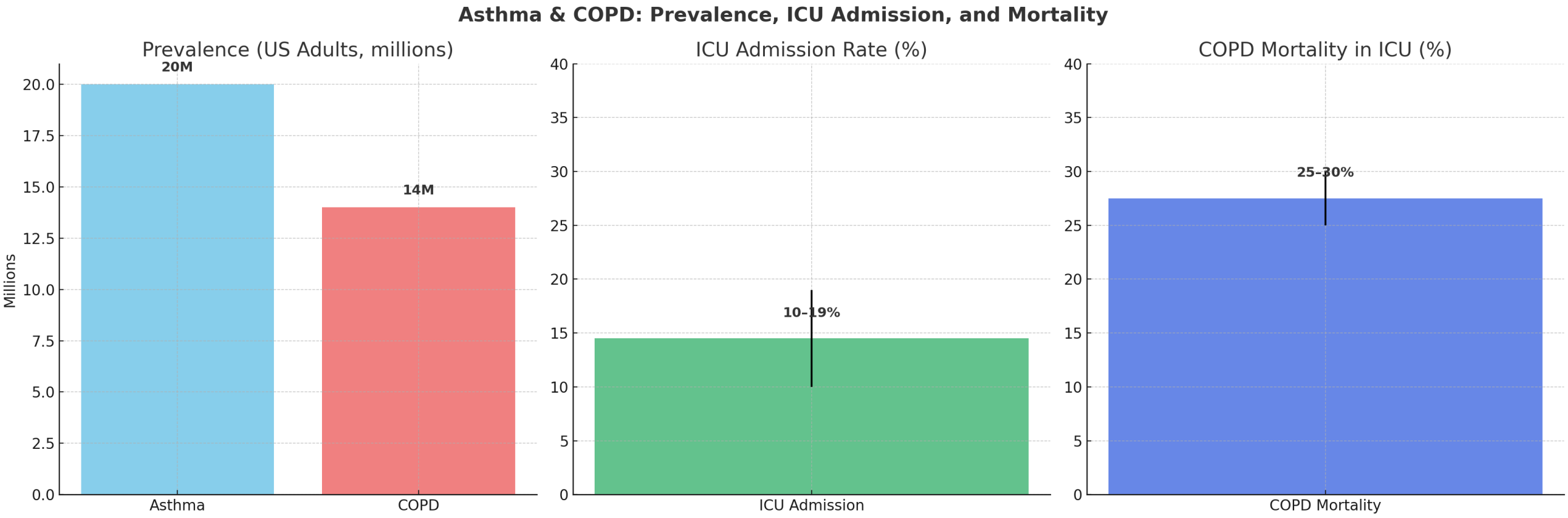
Prevalence, ICU admission, Mortality



asthma 10%

CHEST Crit Care. 2025 Mar;3(1):100107.

Exacerbations Definition

Global Strategy for Asthma Management and Prevention (GINA 2024)

- Asthma exacerbations are defined as episodes of **increased symptoms** (eg, shortness of breath, cough, wheezing) and progressive **decrease in lung function** that require a **change in treatment**.

Pulmonary function tests

- Asthma exacerbation is **defined** as a reduction in **forced expiratory volume (FEV1)** of **more than 20% from baseline**, or a decrease in **peak expiratory flow of >30%** from baseline for **2 consecutive days** at any time during the period of treatment

Defining severe exacerbations

Asthma

- Respiratory rate > 30 breaths/min
- Heart rate > 120 beats/min
- Spo_2 < 90% on ambient air
- PEF ≤ 50% patient's predicted or best

COPD

- Respiratory rate ≥ 24 breaths/min
- Heart rate ≥ 95 beats/min
- Spo_2 < 92% on ambient air (or home oxygen), change > 3% (when known), or both
- Dyspnea VAS ≥ 5
- CRP ≥ 10 mg/L

Mo Med. 2024 Sep-Oct;121(5):364-367
CHEST Crit Care. 2025 Mar;3(1):100107
Eur Respir J. 2012 Feb;39(2):279-89

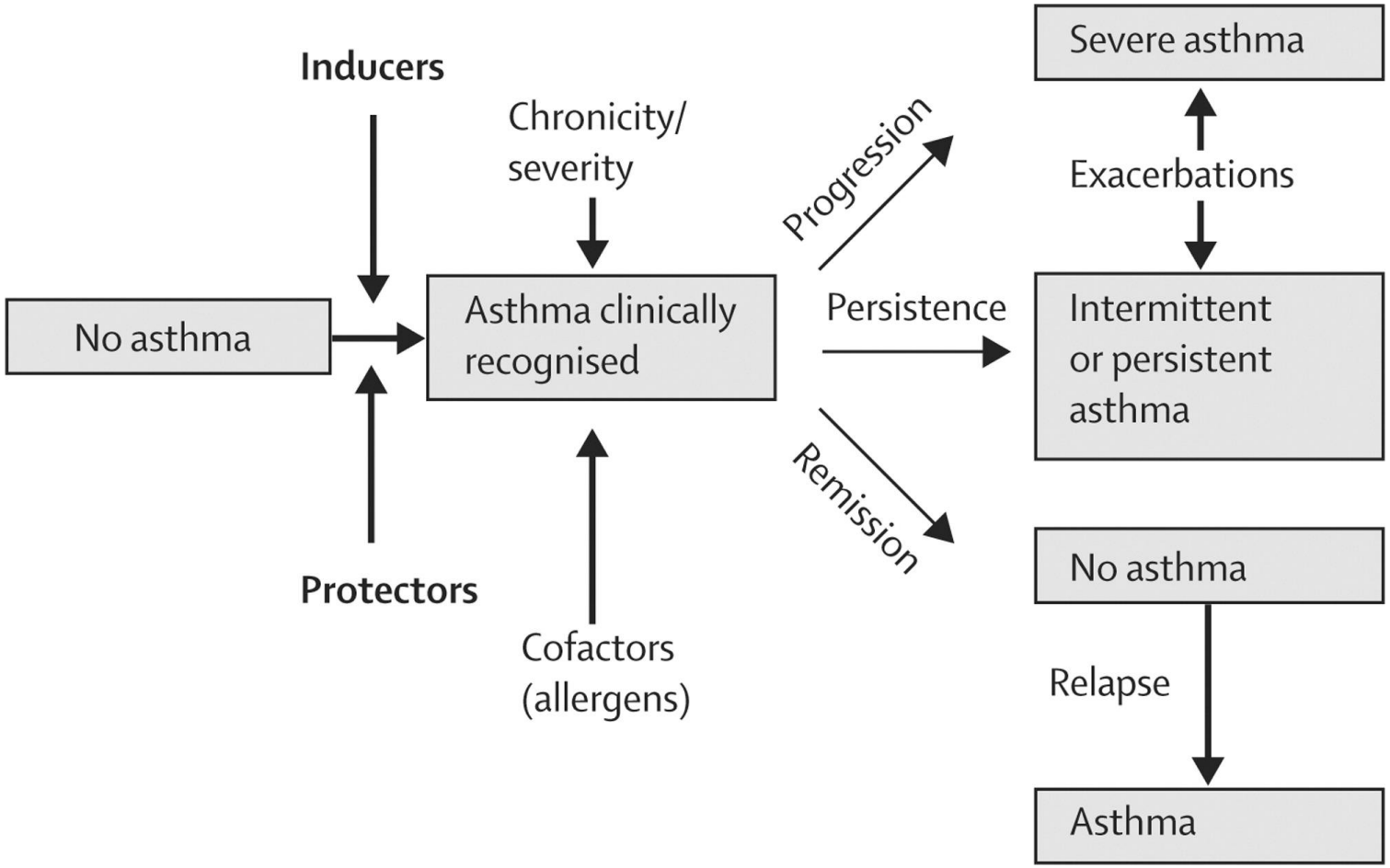
Initial Evaluation

Initial evaluation

- Pulse oximetry to assess SpO_2 and heart rate
- ABG if fatigue or somnolence concerning for hypercapnia, PEF or FEV_1 < 50% predicted, or other clinical concern
- Testing for respiratory viral pathogens
- Sputum bacterial culture
- Initial chest radiograph, ECG, and BNP
- Clinical assessment for PE, consider D-dimer or CTA on case-by-case basis

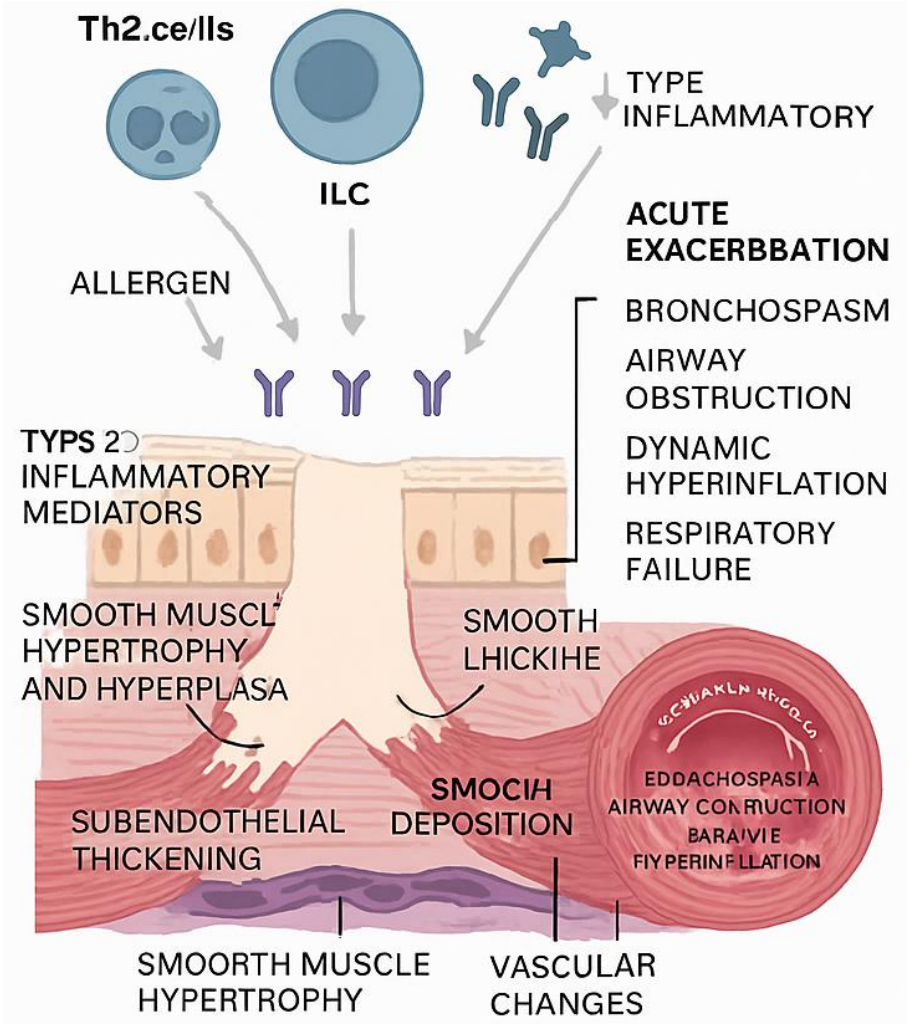
CHEST Crit Care. 2025 Mar;3(1):100107.

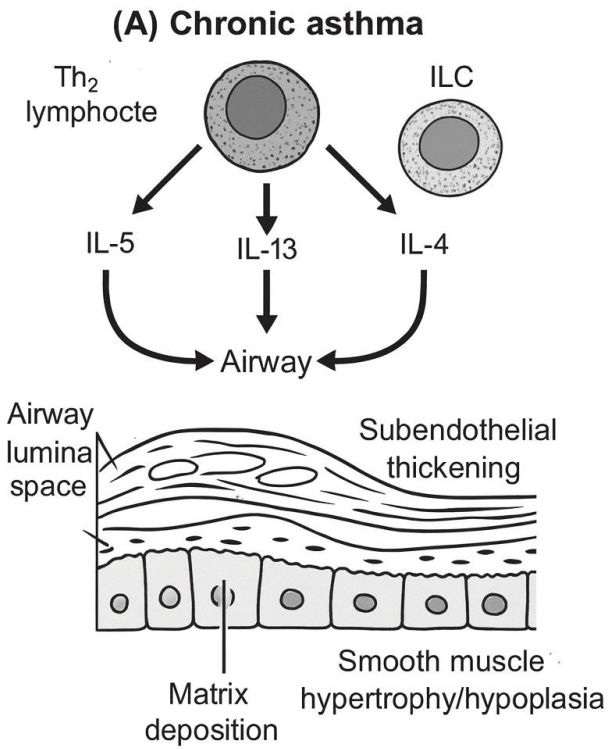
Dynamic disease - Asthma

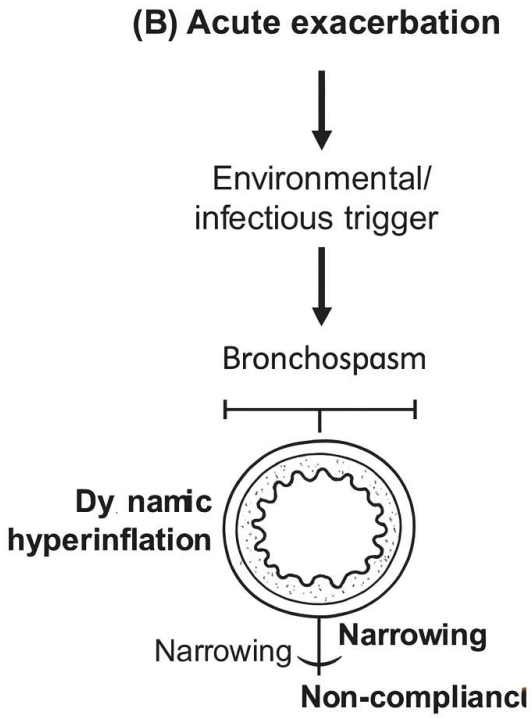


Lancet. 2010 Sep 4;376(9743):826-34.

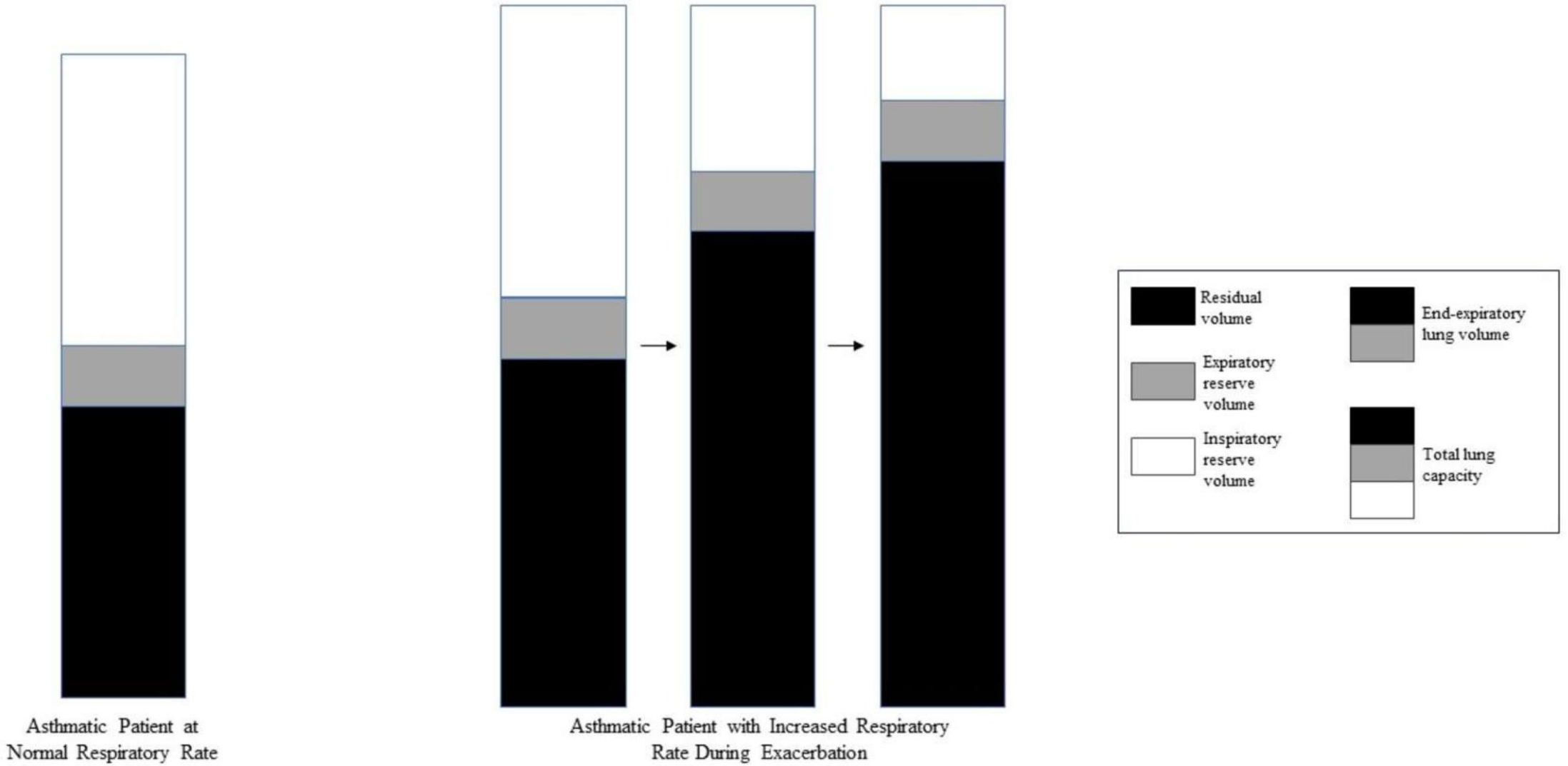
Pathophysiology - *Bronchoconstriction*





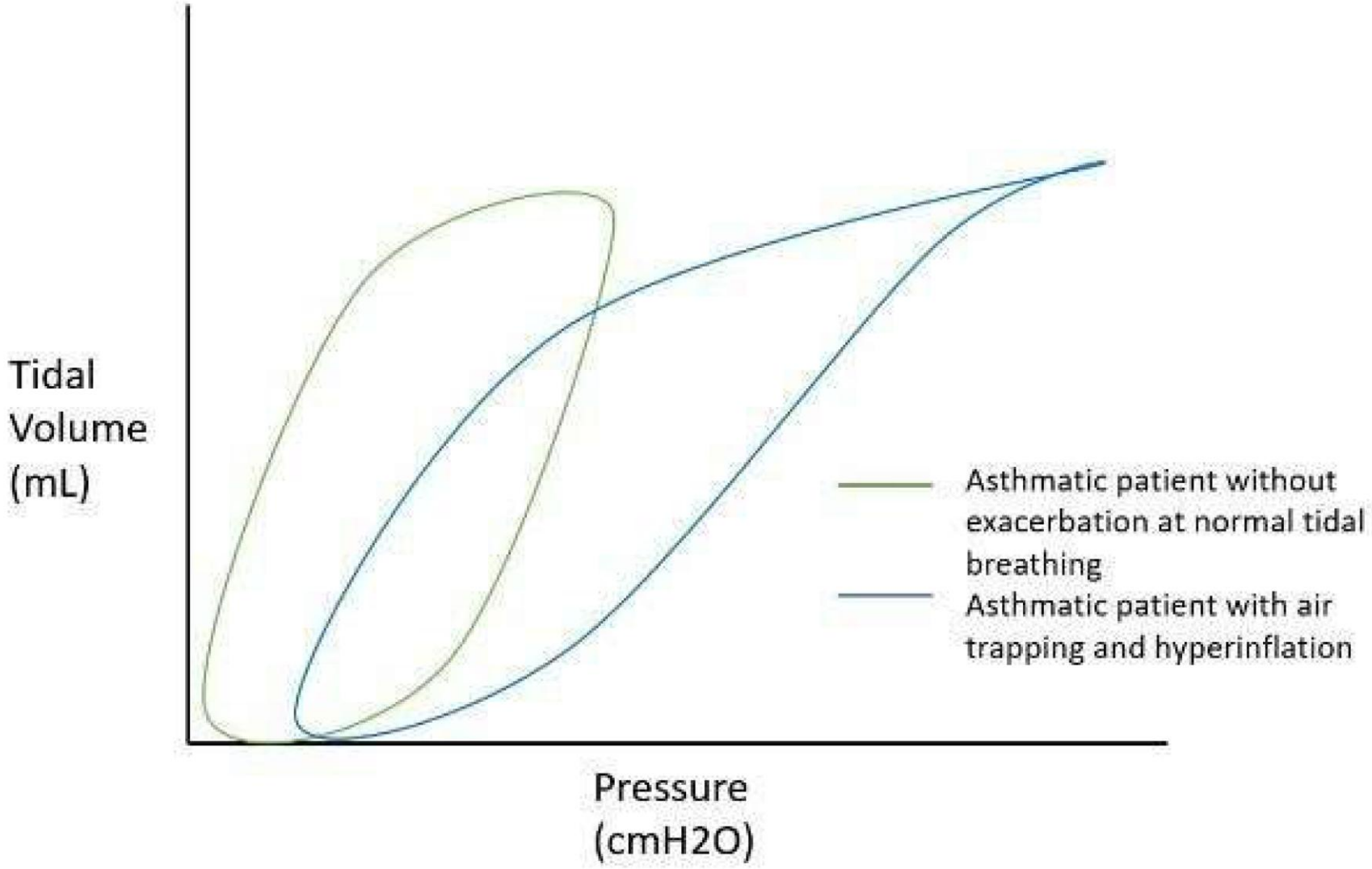


Pathophysiology - *Dynamic Hyperinflation*



J Clin Med. 2024 Feb 1;13(3):859.

Pathophysiology - *Dynamic Hyperinflation*



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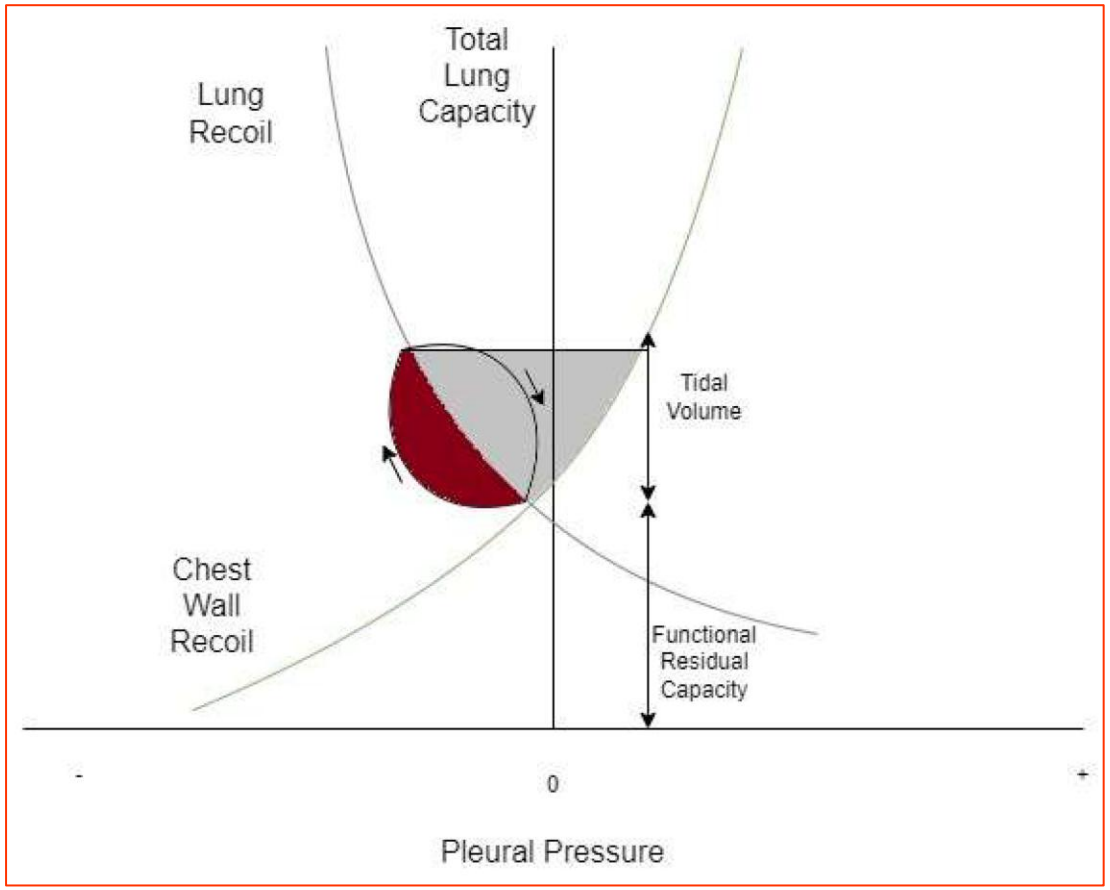
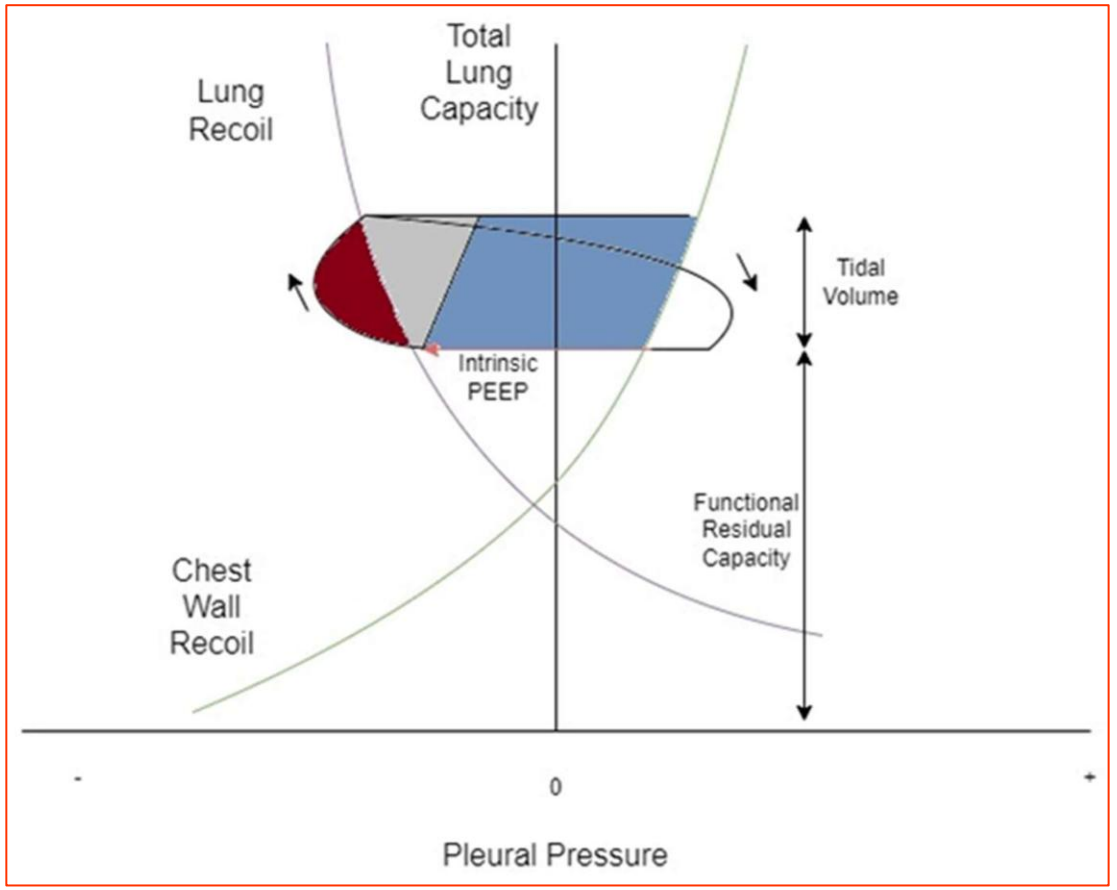
Pathophysiology - *Dynamic Hyperinflation*

Normal



Asthma



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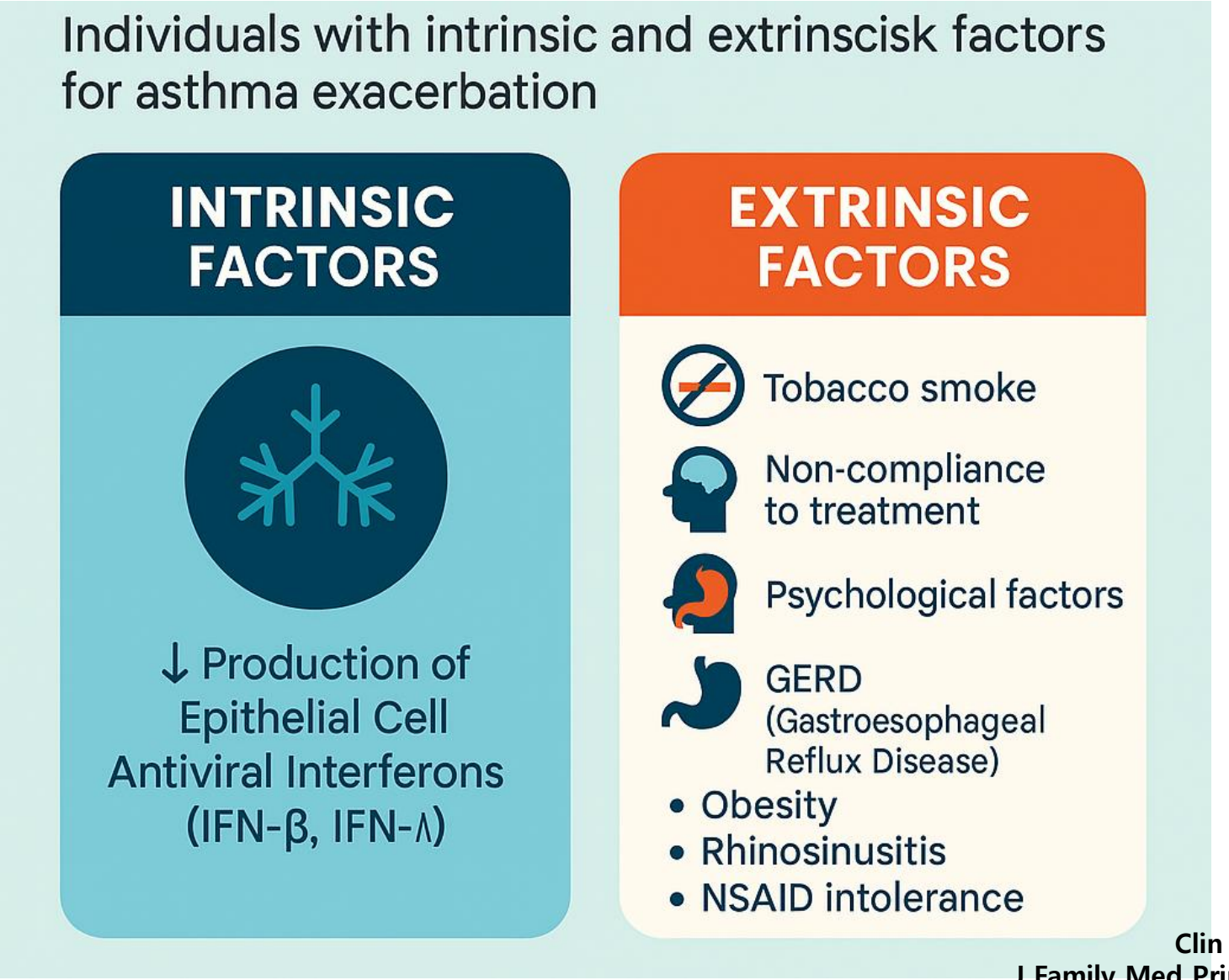
Intrinsic and extrinsic risk factors for asthma exacerbation



Clin Exp Allergy. 2009 Feb;39(2):193-202
J Family Med Prim Care. 2019 Sep 30;8(9):2753-2759

Risk factors for asthma exacerbation - infection

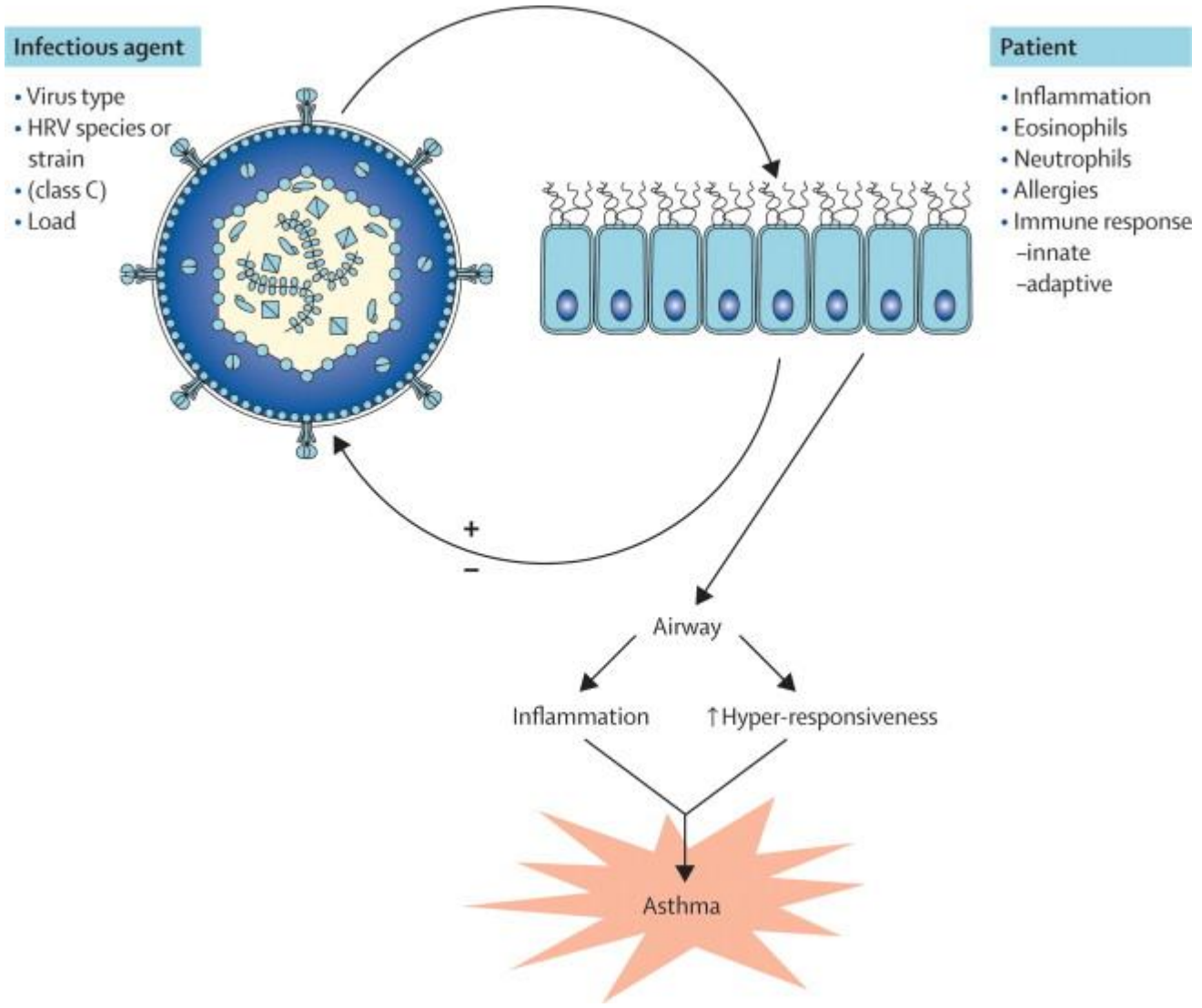
- Studies using **PCR** demonstrated the presence of **viruses** in 80–85% of asthma exacerbations in children and **60–80% of exacerbations in adults**.

- **Viruses** are implicated in **40% to 50%** of asthma and COPD exacerbations.

- Among these agents, **viral infection** is one of the **major drivers** of **asthma exacerbations** accounting for up to 80–90% and **45–80%** of exacerbations in children and **adults** respectively.

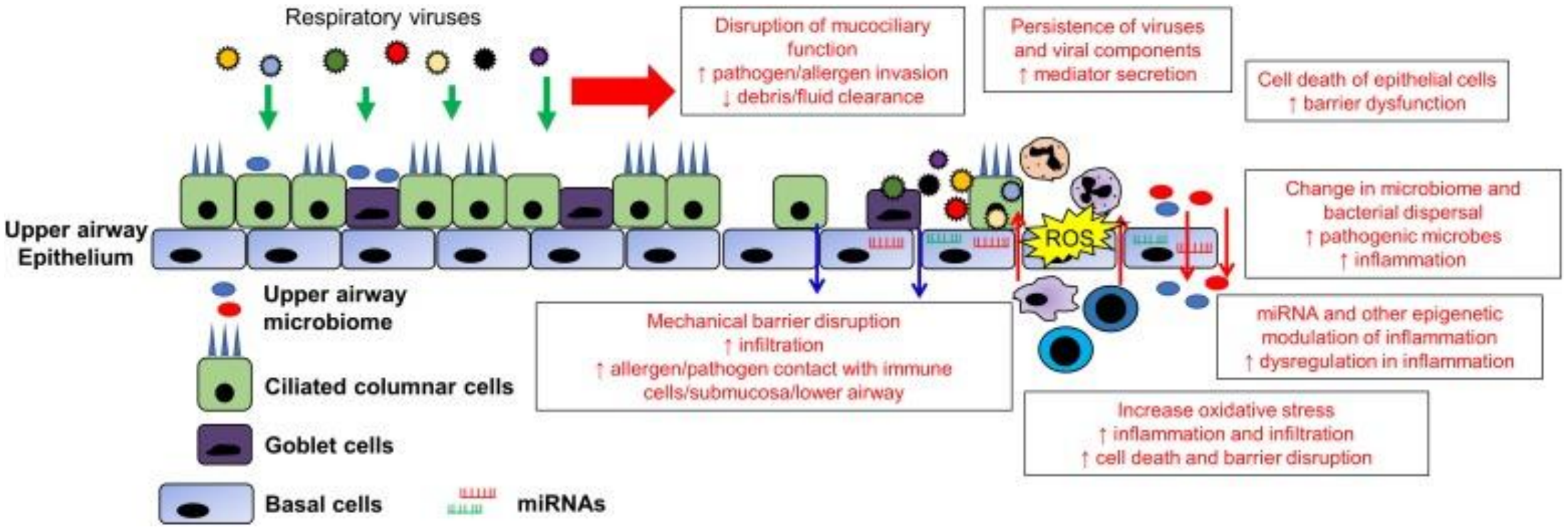
espir Crit Care Med. 2005 Aug 15;172(4):433-9
Am J Respir Crit Care Med. 2005 Aug 15;172(4):433-9
European Respiratory Journal 2010 36(2): 438-445

Mechanisms by which viral infection contributes to asthma exacerbation



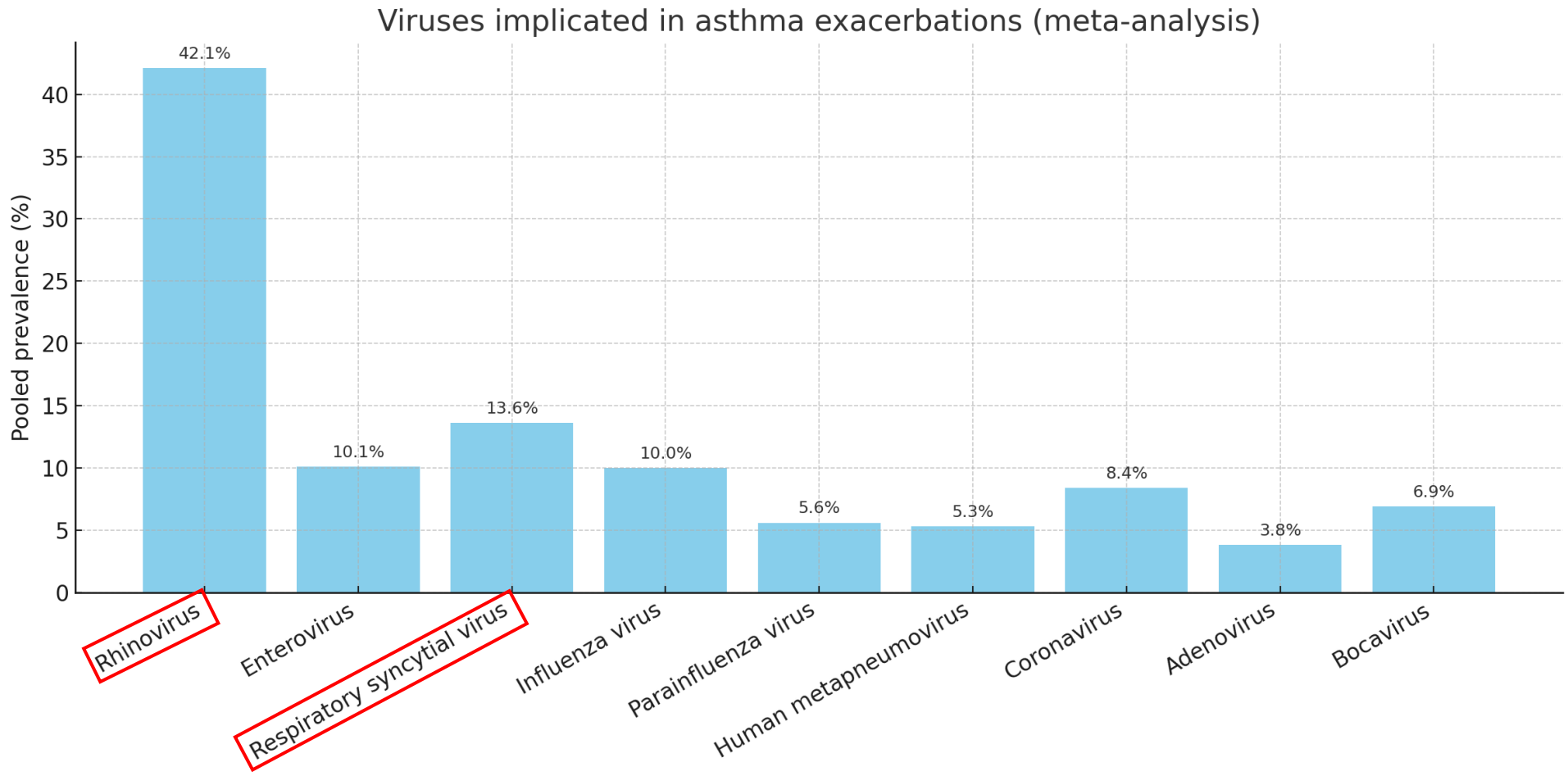
Lancet. 2010 Sep 4;376(9743):826-34.

Pathophysiological processes occurring when respiratory viruses infect upper airway epithelial cells



Front Cell Dev Biol. 2020 Feb 25;8:99.

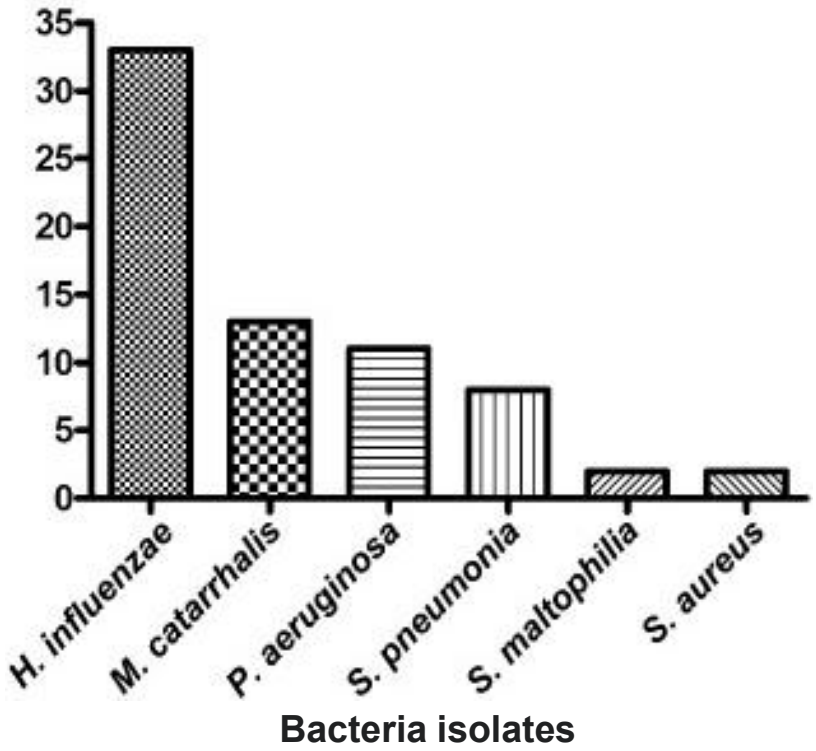
Respiratory Viral implicated in asthma exacerbations



J Allergy Clin Immunol . 2005 Jan;115(1):132-8.
J Allergy Clin Immunol. 2017 Oct;140(4):895-906.
Respir Res. 2019 Sep 13;20(1):210.

Virus and bacterial co-infections in asthma

73% of patients positive for HRV but negative for bacteria at presentation were positive for bacteria when sampled again at day 14
The **effect of dual infection** appears to be associated with **increased severity** during exacerbation.



Eur Respir J. 2014 Jul;44(1):87-96
J Allergy Clin Immunol. 2014 May;133(5):1301-7

Viral and bacterial infection in acute asthma increases the risk of readmission

Univariate for each virus/bacterial combination

	Virus Yes ($n = 83$)	Virus No ($n = 152$)	*t*-test *P*-value
FEV_1 at presentation (% predicted), mean (SD)	43 (19.4)	45 (18.6)	0.3
ACQ6, mean (SD)	3.4 (1.5)	3.8 (1.5)	0.2
LOS, days mean (SD)	5 (2.5)	3.4 (2.5)	<0.001
Readmission, *n*	22	17	0.003
FEV_1 at recovery % change from pre-exacerbation, mean (SD)	−4.8% (1.7)	−2.1% (2.3)	0.02

	Bacteria Yes ($n = 45$)	Bacteria No ($n = 190$)	
FEV_1 at presentation (% predicted), mean (SD)	34 (19.3)	47 (19.6)	<0.001
ACQ6, mean (SD)	3.7 (1.5)	3.1 (1.5)	0.4
LOS, days mean (SD)	5.6 (2.8)	3.6 (2.5)	0.001
Readmission, *n*	22	21	<0.001
FEV1 at recovery % change from pre-exacerbation, mean (SD)	−3.6% (1.5)	−2.4% (1.9)	0.4

	Virus and bacteria Yes ($n = 19$)	Virus and bacteria No ($n = 216$)	
FEV_1 at presentation (% predicted), mean (SD)	32 (19)	46 (14)	0.001
ACQ6, mean (SD)	3.6 (1.5)	3.6 (1.2)	0.9
LOS, days mean (SD)	6.9 (3.1)	3.7 (2.6)	<0.001
Readmission, *n*	16	2	<0.001
FEV_1 at recovery % change from pre-exacerbation, mean (SD)	−5.9% (1.7)	−1.9% (2.3)	0.01

Multivariate logistic regression for independent factors determining length of stay

Variables	Odds ratio	95% CI	z	*P* > z
Virus	3.0	1.16, 7.6	2.28	0.02
Bacteria	0.8	0.2, 3.1	−0.31	0.9
Virus and bacteria	5.5	0.4, 69	1.31	0.3
Age	0.98	0.95, 1.01	−1.5	0.1
Gender	3.2	1.3, 7.9	2.5	0.01
Smoking status	1.8	1.0, 3.1	2.06	0.8
ICS BDP/day	0.99	0.99, 1.0	−1.4	0.04
FEV_1 (% predicted)	0.96	0.94, 0.99	−2.5	0.03
COPD	4.6	1.7, 12.5	3.02	0.003

Multivariate logistic regression for independent factors determining readmission

Variables	Odds ratio	95% CI	z	*P* > z
Virus	0.9	0.2, 4.7	−0.1	0.9
Bacteria	2.3	0.4, 12.9	0.3	0.3
Virus and bacteria	32.2	1.1, 93	2.02	0.04
Age	1.0	0.51, 1.02	0.08	0.9
Gender	0.6	0.1, 2.8	−0.7	0.6
Current smoker	1.3	0.5, 3.2	0.3	0.6
ICS BDP/day	1.0	0.99, 1.0	0.4	0.7
FEV_1 (%predicted)	0.91	0.85, 0.97	0.004	0.004
COPD	2.7	0.5, 10.8	0.2	0.2

The important independent role of **virus infection** along with **viral/bacterial co-infection** as **independent predictors of acute severity in asthma** and for the first time demonstrate that those with **co-infection** are also more likely to be **readmitted to hospital** following their exacerbation.

Respirology. 2013 Jul 25;18(6):996–1002

Pharmacologic Management

Bronchodilators - *Treating Bronchospasm in Acute Severe Asthma*

Short-acting β2-Agonists (SABA, e.g., Albuterol)

- **Cornerstone therapy** for acute exacerbations.
- **Continuous nebulization**: more consistent drug delivery, possible benefit in children with severe asthma (status asthmaticus).
  - In adults: **no difference** in safety, morbidity, or mortality vs intermittent dosing.
- **Dose–response titration** may be helpful (variable response).
- **Adverse effects:**
  - High-dose → **type B lactic acidosis** (not due to tissue hypoperfusion).
  - IV β-agonists: **no added benefit vs inhaled**; side effects ↑ (hypokalemia, myocardial ischemia, CV events).

Anticholinergics (e.g., Ipratropium bromide)

- Mechanism: block muscarinic receptors → bronchodilation + mucus secretion ↓.
- Onset: slower (peak at 60–90 min).
- **Evidence:**
  - In ED: SABA + ipratropium → hospitalizations ↓ in moderate–severe exacerbations.
  - **No evidence** for routine use in hospitalized adults with severe asthma.

IV Magnesium Sulfate

- Mechanism: Ca^{2+} channel blockade → smooth muscle relaxation, bronchodilation.
- Dose: **2 g IV**.
- **Adults:** shown to improve pulmonary function, generally safe.

J Clin Med. 2024 Feb 1;13(3):859.

Corticosteroids - *Treating Airway Inflammation in Acute Severe Asthma*

Indications

- Recommended for **severe asthma and COPD exacerbations** not responding to initial bronchodilator therapy.

Evidence

- **Asthma & COPD in acute care settings**:
  Strong evidence supporting corticosteroids (relapse ↓, treatment failure ↓)

Recommended Regimen

- **Asthma:** Prednisone **1 mg/kg/day** (up to 50 mg/day) × **5–7 days**.

COPD: Prednisone **40 mg/day × 5 days**.
Shorter courses (**5–7 days**) are as effective as longer courses (**10–14 days**) and reduce risk of **pneumonia and death**.

- **Critically ill patients (mechanical ventilation required):**
  Limited evidence.
  Some studies: reduced duration of IMV and lower NIV failure.
  Others: no significant difference in outcomes.

High-Dose Corticosteroids

- Critically ill studies often used higher doses (methylprednisolone >240 mg/day)
  - Increased treatment failure
  - Longer IMV duration
  - Prolonged ICU/hospital stay
  - Adverse events: hyperglycemia requiring insulin, fungal infections

Antibiotics

Asthma

•Evidence:

- RCTs: No benefit in symptoms or lung function with antibiotics
- Retrospective study: Early antibiotics composite treatment failure ↓ (IMV, ICU transfer, mortality, readmission)

•Recommendation:

- Use only if **critically ill with suspected concurrent lung infection**.
- No evidence to support routine use → aligns with **GINA** guidelines.

COPD

•Indications:

- Critically ill patients with:
  - Increased **dyspnea, sputum volume, and purulence** (all 3 or ≥2 if purulence present), OR
  - Requirement for mechanical ventilation (NIV/IMV).

•Benefits:

- ↓ treatment failure
- ↓ mortality
- Greatest effect in patients with **sputum purulence** (marker of bacterial load).

•Choice of Antibiotics:

- **Macrolides or tetracyclines** = first-line
- Consider **antipseudomonal agent** if risk factors for *Pseudomonas*.

•Duration:

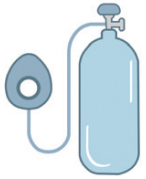
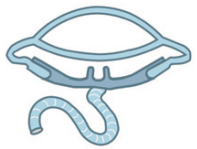
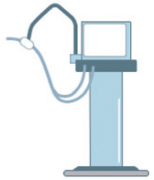
- **5–7 days** (longer courses do not improve outcomes).

•Biomarkers:

- Current evidence insufficient for routine use of **CRP** or **procalcitonin** to guide therapy.

Oxygen Management

Supplemental Oxygen

	 Supplemental O_2	 HFNT	 NIV	 IMV	 VV ECMO
Indications	Spo_2 < 92% in asthma Spo_2 < 88% in COPD	Severe dyspnea with respiratory distress (eg, accessory muscle use) Persistent hypoxemia despite O_2	Severe dyspnea with respiratory distress Persistent hypoxemia despite O_2 $PaCO_2$ ≥ 45 mmHg and pH ≤ 7.35	Cardiac arrest/HD instability Inability to tolerate NIV or worsening respiratory failure despite NIV Altered consciousness Massive aspiration or persistent vomiting	Hypercapnic respiratory failure (pH < 7.25) despite optimal IMV Hypoxemic respiratory failure despite optimal IMV Hemodynamic compromise from hyperinflation
Initial Settings	Titrate 1-15 L/min flow to target Spo_2 93%-95% in asthma and Spo_2 88%-92% in COPD	Flow 15-60 L/min; use higher flow to obtain a PEEP of 3-5 cm H_2O Titrate Fio_2 to target Spo_2 93%-95% in asthma and Spo_2 88%-92% in COPD	Titrate PS to target V_T of 6-8 mL/kg IBW Initial PEEP approximately 5 cm H_2O Titrate Fio_2 to target Spo_2 93%-95% in asthma and Spo_2 88%-92% in COPD	V_T 6-8 mL/kg RR, 10-12 breaths/min PEEP, 0-10 cm H_2O Titrate Fio_2 to Spo_2 goal I:E ratio between 1:2 and 1:4 Flow rate, 60-100 L/min Trigger sensitivity, −1 to −2 cm H_2O or 2 L/min[a]	Titrate 2-6 L/min flow to Spo_2 goal Titrate FDO_2 to Spo_2 goal Sweep 1-9 L/min, titrate to reduce $PaCO_2$ by < 20 mmHg in first 24 h
Complications	Hyperoxia associated with increased mortality in COPD Epistaxis	Claustrophobia/discomfort Impaired swallow function and risk of aspiration	Claustrophobia/discomfort Skin breakdown at mask interface Gastric distention/risk of aspiration	Barotrauma (eg, pneumothorax) Ventilator-associated pneumonia ETT complications (eg, tracheal stenosis) Muscle weakness	Hemorrhage Thrombosis Infection Cannulation complications (eg, vascular perforation)

Non-Invasive Ventilation

Asthma

•**Evidence limited**:

- Few RCTs, underpowered for IMV prevention or mortality benefit.
- ERS/ATS: **No formal recommendation** for routine NIV in acute asthma.

•**Trends:**

- Use ↑ from 18.5% (2010) → 29.9% (2017).
- Large cohort (53,654 pts): NIV ↓ odds of IMV and mortality.

Practical Considerations

<u>No universally accepted criteria for initiation in asthma</u>

COPD

•Strong evidence:

- ↓ Need for IMV
- ↓ Mortality

•Standard of care in acute COPD exacerbations with respiratory failure.

Physiological Effects

•**CPAP:** bronchial diameter ↑

•**BiPAP:** FEV1 and PEFR ↑, especially with bronchodilators ↑

•**Muscle unloading:** work of breathing ↓, accessory muscle use ↓, less fatigue.

Non-Invasive Ventilation

Table 1. Randomized controlled trials investigating non-invasive ventilation in acute asthma.

Study	Number of Patients	Outcome
Pollack et al., 1995 [34]	40 patients in conventional nebulizer group, 60 patients in BiPAP group	ED management with NIV to deliver bronchodilators resulted in statistically significant improvement to peak expiratory flow rate (PEFR)
Holley et al., 2001 [35]	19 patients in NIV group, 16 in standard of care group	Trend toward decreased need for mechanical ventilation and decreased length of hospital stay in NIV group.
Soroksky et al., 2003 [36]	15 patients in NIV and conventional therapy group, 15 patients in conventional-therapy-only group	In patients with severe acute asthma, NIV showed statistically significant improvement to FEV1, and a reduction in need for hospitalization.
Gupta et al., 2010 [37]	28 patients in NIV and conventional therapy, 25 patients in conventional-therapy-only group	More patients receiving NIV experienced >50% improvement in FEV1 at 1, 2, 4 h compared to conventional therapy group, although not statistically significant. Significantly shorter ICU stay in NIV group.
Soma et al., 2008 [38]	16 patients with IPAP 8 cm H_2O and EPAP 6 cm H_2O, 14 patients with IPAP 6 cm H_2O and EPAP 4 cm H_2O), and 14 patients in conventional-therapy-only group	Statistically significant improvement to FEV1 in high-pressure group only compared to conventional therapy group. Significant improvement to dyspnoea as measured by Borg scale in high- and low-pressure groups compared to conventional therapy group.
Brandao et al., 2009 [39]	24 patients in NIV group (12 IPAP 15 cm H_2O EPAP 5 cm H_2O and 12 IPAP 15 cm H_2O EPAP 10 cm H_2O)	Statistically significant improvement to PEFR and FVC in high-EPAP group. Statistically significant improvement in PEFR and respiratory rate in the low-EPAP group compared to conventional therapy group.
Galindo-Filhr et al., 2012 [40]	11 patients received NIV and conventional therapy and 10 patients received conventional therapy	Statistically significant improvement in respiratory rate, FEV1, FVC, PEFR and IC in NIV group compared to conventional therapy group.

BiPAP: bi-level positive airway pressure; ED: emergency department; EPAP: expiratory positive airway pressure; FEV1: forced expiratory volume in 1 s; FVC: functional vital capacity; IC: inspiratory capacity; ICU: intensive care unit; IPAP: inspiratory positive airway pressure; NIV: non-invasive ventilation; PEFR: peak expiratory flow rate.

J Clin Med. 2024 Feb 1;13(3):859.

Non-Invasive Ventilation - Indications and contraindications for NIV initiation in acute asthma exacerbations.

Table 2. Indications and contraindications for NIV initiation in acute asthma exacerbations.

Indications
Respiratory Rate > 25 breaths per minute
Heart Rate > 110 beats per minute
Accessory Respiratory Muscle Use
Hypoxemia with P/F ratio > 200
Hypercapnia with partial pressure carbon dioxide ($PaCO_2$) < 60 mm Hg
FEV1 < 50% predicted following ≥ 2 consecutive nebulized bronchodilators
Absolute Contraindications
Decreased alertness
High risk for aspiration
Circumstances precluding proper mask seal
Physical restraints due to agitation
Lack of properly trained staff
Relative Contraindications
Hemodynamic instability
Severe hypoxemia (P/F ratio < 200)
Severe hypercapnia ($PaCO_2$ > 60 mm Hg)

FEV1: forced expiratory volume in 1 s; P/F: partial pressure of oxygen to fraction of inspired oxygen ratio; $PaCO_2$: partial pressure of carbon dioxide.

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Mechanical Ventilation in Severe Acute Asthma Exacerbations

Table 3. Ventilator strategies in severe asthma exacerbations.

Ventilator Strategy	Effect
Controlled hypoventilation with low respiratory rate [46]	Hypercapnia without deleterious effects; no pneumothorax or mortality
Lower vs. higher minute ventilation— 10 L/min vs. 16 L/min vs. 26 L/min [47]	Increase in pulmonary hyperinflation, risk of hypotension and barotrauma at higher minute ventilation
Increased inspiratory flow and square waveform [47,48]	Reduced inspiratory time, prolonged I:E ratio but with minimal expiratory prolongation; minimal impact on hyperinflation at lower minute ventilation
Extrinsic PEEP application [49]	Applied PEEP worsened hyperinflation, hypotension without decreasing auto-PEEP

I:E: inspiratory:expiratory; PEEP: Positive end-expiratory pressure.

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Mechanical Ventilation in Severe Acute Asthma Exacerbations

Indications for IMV

- Respiratory arrest
- Extreme respiratory muscle fatigue
- Encephalopathy
- Worsening **respiratory acidosis** or progressive fatigue
- **NIV failure** → proceed to intubation & IMV

Ventilator Settings & Strategies

- **Modes:** Pressure control OR volume control
- **Goal:** Reduce air trapping & hyperinflation
  - **Low minute ventilation** → allow full exhalation
  - **I:E ratio: 1:4 – 1:5**
  - **Respiratory rate:** ~12–14 breaths/min
- **Effect:** Prolonged exhalation air trapping ↓ → EELV ↓, auto-PEEP, alveolar pressure, dynamic hyperinflation

Assessing Pulmonary Hyperinflation

- **Plateau pressure (Pplat):**
  - Measured during inspiratory hold
  - Reflects hyperinflation (normal compliance in asthma)
  - Target: **Pplat < 30 cmH_2O**

- **Auto-PEEP:**
  - Measured during expiratory hold
  - May reach ≥ 10 cmH_2O
- **Requirement:** sedation & synchrony to perform manoeuvre, avoid patient-triggered breaths

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Extubation Strategies

General Readiness

•Same criteria as other respiratory diseases:

- Improvement of underlying obstruction
- Ability to follow commands (spontaneous awakening trial)
- Respiratory stability on **spontaneous breathing trial** with minimal support

Asthma

•Optimal post-extubation support is **uncertain**.

•Evidence lacking on whether to use NIV or HFNT.

COPD

•Preferred strategies after extubation:

- **NIV** (same settings as during IMV) OR
- **HFNT**
- Both ↓ mortality, ↓ reintubation, ↓ IMV duration.

•NIV vs HFNT:

- Similar effectiveness overall
- NIV may be better for **high-risk patients**

•NIV + HFNT alternating > HFNT alone (useful for NIV intolerance).

CHEST Crit Care. 2025 Mar;3(1):100107.

ECMO

Indications

•Severe asthma exacerbation with **persistent CO_2 retention** despite optimal IMV & pharmacologic therapy.
•**CO_2 retention syndromes** (bronchospasm, airflow obstruction) → ineffective ventilation, PIP ↑, risk of barotrauma & hemodynamic instability.
•Early VV-ECMO may minimize adverse effects of IMV.
•**$ECCO_2R$** (extracorporeal CO_2 removal): adjunct option for hypercapnia → improves $PaCO_2$, reduces need for intubation, minimizes hyperinflation.

Management

•**Rest ventilator settings:**
- Extremely low minute ventilation
- Minimization of hyperinflation

•**VV-ECMO function:** provides CO_2 removal ± oxygenation.
•**CO_2 clearance:** proportional to sweep gas flow (50–80 mL/kg/min), titrated to pH & $PaCO_2$.
•Caution: Rapid CO_2 removal → risk of neurologic injury (mainly in chronic hypercapnia).
•As bronchospasm resolves → ventilator/ECMO settings optimized → eventual decannulation.

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Monitoring the Critically Ill Asthmatic Patient

Table 4. Monitoring entities and their usefulness in severe asthma.

Monitoring Entity	Usefulness
Pulse Pressure monitoring	Dynamic marker of threatened cardiac output, the combined effect of dynamic hyperinflation, and may result in decreasing cardiac output through decreased venous return and direct compression of the cardiac chambers.
Urine Output	Surrogate for effective tissue perfusion. Urine output is a direct marker for end-organ function and a decrease could precede the development of hemodynamic shock. Provides an early marker for intervention in most situations
Daily Cardiac Output estimation and RV function using point of care ultrasound (POCUS)	Daily assessment of RV function and estimation of cardiac output is valuable in patients on mechanical ventilation because of the complex interaction between the cardiac and pulmonary systems in response to positive pressure ventilation. Assessment of intravascular volume and the effects of dynamic hyperinflation can be readily apparent.
P_{peak}	While absolute P_{peak} values are less valuable in bronchospasm, establishing a trend may be useful to assess response to therapy
auto-PEEP	Total PEEP measurement using an end-inspiratory hold manoeuvre is necessary for patients with a high risk of developing dynamic hyperinflation and provides a direct measure of auto-PEEP; this information in the context of invasive hemodynamic monitoring is a useful guide to titration of ventilatory strategies.
Airway resistance	Many current ventilators are able to measure airway resistance in addition to the pressures described above; establishing a trend of airway resistance can help assess response to therapy.
Chest radiograph	Due to the high risk of pneumothorax associated with mechanical ventilation in status asthmaticus, frequent chest radiographs may be useful. In addition, monitoring of indwelling catheters, endotracheal tubes, and ECMO cannulae may be necessary depending on the clinical context.
Lung Ultrasound	The presence of A-lines with lung sliding in the anterolateral regions without alveolar consolidations or pleural effusions in the posterolateral areas (A-profile without PLAPS) may be useful for diagnosis and monitoring for development of complications of NFA including pneumothorax, pneumonia, and pulmonary oedema [80].

ECMO: extracorporeal membrane oxygenation; NFA: near-fatal asthma; PEEP: positive end-expiratory pressure; PLAPS: posterolateral alveolar and/or pleural syndrome; POCUS: point of care ultrasound; P_{peak}: peak pressure; RV: right ventricle.

J Clin Med. 2024 Feb 1;13(3):859.

Preventive Therapies to reduce exacerbations

Preventive Therapies to reduce exacerbations

- **long-term preventive therapies** to reduce the frequency of exacerbations
- treatments commenced **after the onset of an exacerbation**

- **Types of Preventive Treatment**

I. Inhaled corticosteroids (ICSs)

II. Inhaled bronchodilators including long-acting beta agonists (LABAs) and long-acting muscarinic receptor antagonists (LAMAs), and combinations of these

III. Biologic Therapies

IV. Inhaled IFN-β

V. Antiviral agents

Ther Adv Respir Dis. 2016 Apr;10(2):158-74.

Preventive treatments – Inhaled Corticosteroids

Inhaled Corticosteroids (ICSs)

- **Mainstay treatment** → modulate adaptive immune response
- **Clinical trials**: effective at reducing exacerbations
- **Virus-induced exacerbations**: effects unclear

  In atopic asthmatics: Budesonide improved airway hyperresponsiveness & eosinophilia, but did not prevent HRV 16-induced inflammation

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Preventive treatments – Biologic Therapies

Biologic Therapies

- Target **Th2 cytokines** (IL-4, IL-5, IL-13) and **IgE**
- **Benefits**
  - Improved lung function
  - Reduced symptoms
  - Lower OCS requirements
  - Significant reduction in exacerbations

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Preventive treatments – Biologic Therapies

Anti-IgE
•Omalizumab
- Mechanism: IgE blockade → ↓ serum IgE
- Evidence: **58% reduction** in exacerbations in atopic asthma (IgE >30 IU/ml on ICS)

Anti-IL-5
•Mepolizumab, Reslizumab
- Target: IL-5 (eosinophilic pathway)
- Evidence: ~**50% reduction** in exacerbations vs placebo

Anti-IL-13
•Lebrikizumab, Tralokinumab
- Uncontrolled asthma: **no overall reduction** in exacerbations
- **Biomarker-driven effect (periostin):**
  - Periostin-high → **60% reduction**
  - Periostin-low → minimal effect

Anti-IL-4Rα
•Dupilumab (blocks IL-4 & IL-13 signaling)
- Evidence: **87% reduction** in exacerbations (OR 0.08, $p<0.001$)
- Tested in moderate–severe asthma on combination therapy

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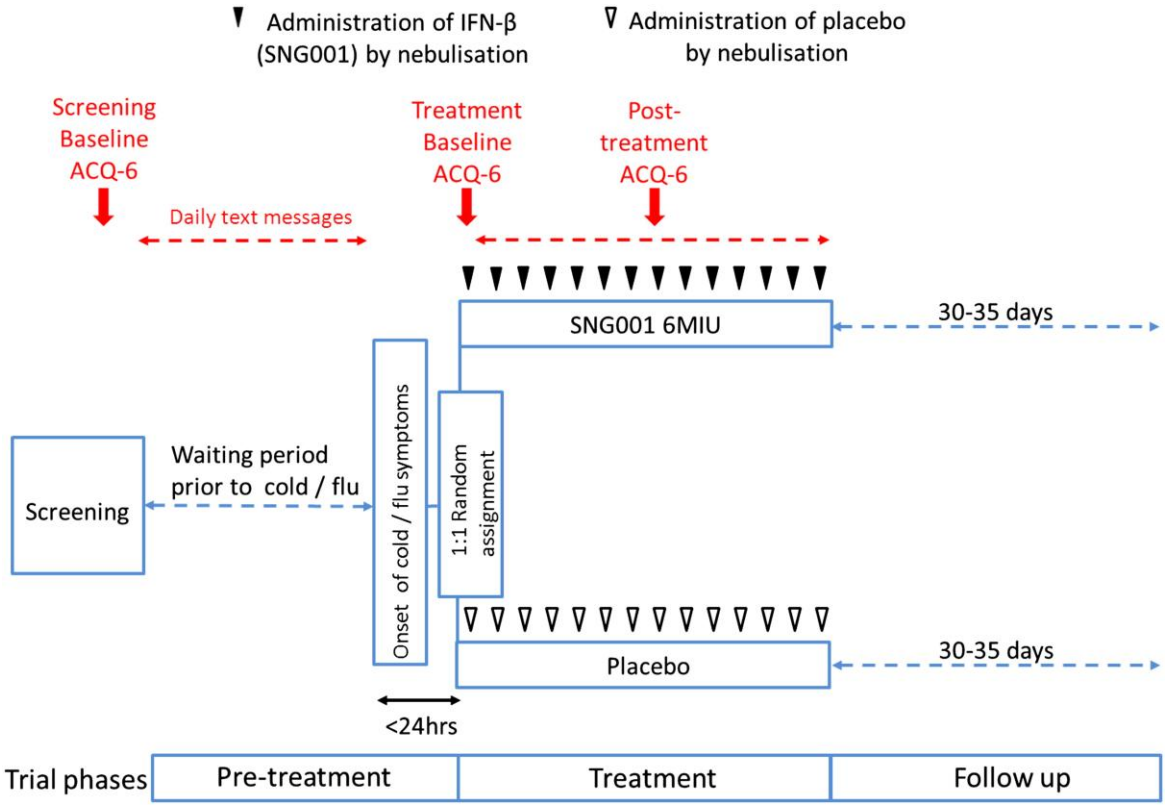
Preventive treatments – inhaled IFN-β

Rationale: *Ex vivo*, bronchial epithelial cells from people with asthma are more susceptible to rhinovirus infection caused by deficient induction of the antiviral protein, IFN-β. Exogenous IFN-β restores antiviral activity.

- **Randomized, Double-blind, Placebo-controlled**
- Patients with history of **URTI-induced asthma exacerbations**
- Enrolled when reporting cold/flu symptoms (Jackson/Predy criteria)

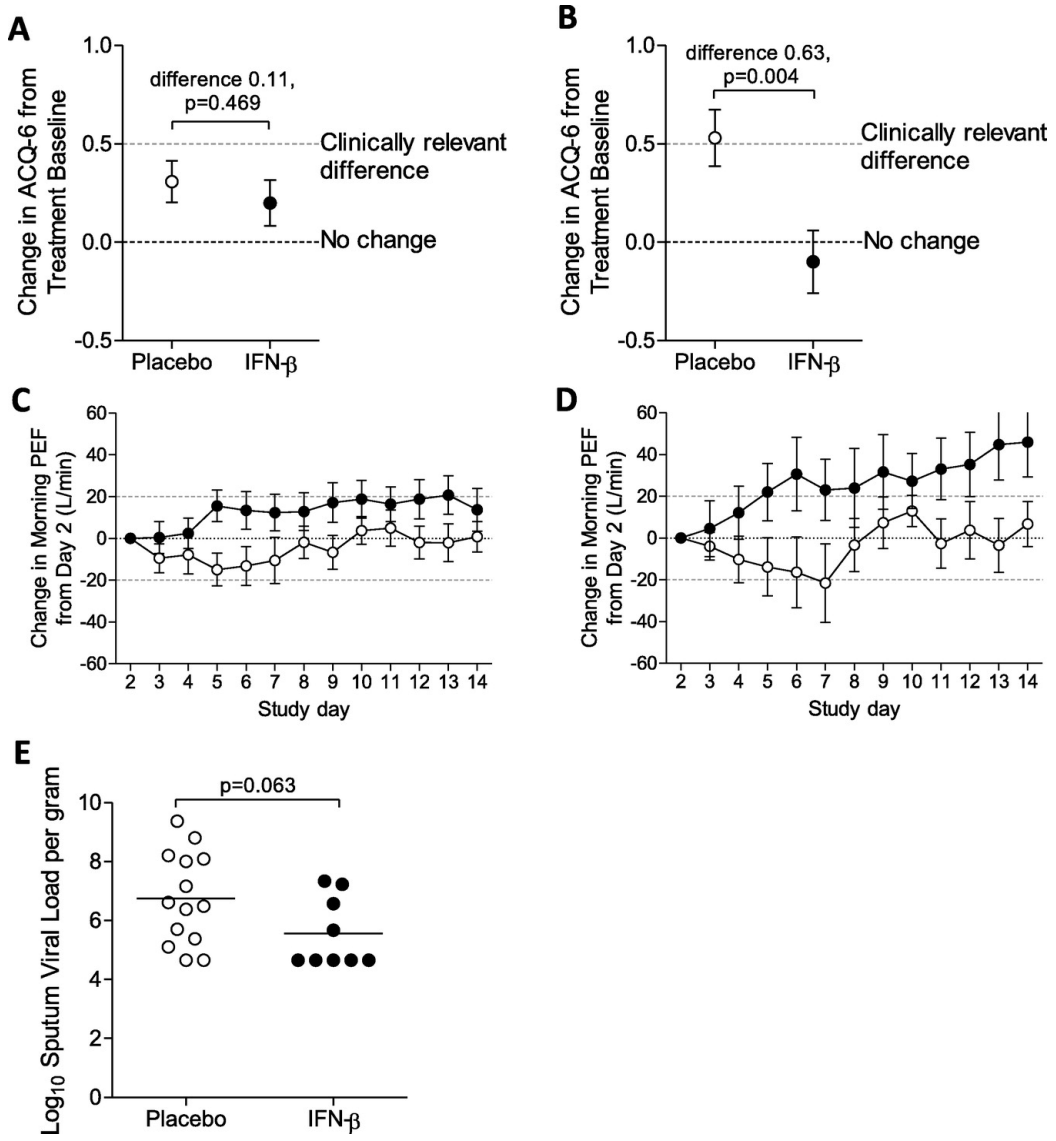
- **Intervention**
- **Inhaled IFN-β (SNG001) vs Placebo**
- Randomization 1:1
- **Dosing:** Once daily × 14 days
- **Start:** Within 24 hours of URTI symptom onset

- **Primary:** Mean change in **ACQ-6** (baseline → Day 8, mITT population)
- **Secondary:** PEF, symptom diaries, biomarker response



Am J Respir Crit Care Med. 2014 Jul 15;190(2):145-54

Preventive treatments – inhaled IFN-β



Findings

- **Asthma symptoms:** No significant improvement vs placebo
- **Morning peak expiratory flow:** Improved (p = 0.033)
- **Innate immunity:** Enhanced antiviral activity (serum CXCL10 ↑)
- **Moderate-to-severe subgroup:**
  - Significant ↓ in **ACQ-6 score** (p = 0.004)
  - Suggests greater benefit in more severe asthma

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Preventive treatments – Antiviral agents

Targeting HRV

ICAM-1 blockade

- **Tremacamra (soluble ICAM-1):**
  - RCT: ↓ symptoms vs placebo ($p<0.001$), effective pre- and post-inoculation.
- **14C11 (anti–ICAM-1 antibody):**
  - Mouse model: inhibited HRV-induced asthma exacerbations.
  - Did **not impair host defence** via LFA-1/ICAM-1 pathway.
- **Implication:** ICAM-1 blockers may help prevent asthma/COPD exacerbations → need more clinical studies.

Capsid Inhibitors

- **Pleconaril (oral, capsid-function inhibitor):**
  - Large RCT in healthy adults: shortened illness by ~1 day.
  - Issues: significant **drug–drug interactions** (e.g., oral contraceptives).
  - **FDA did not approve**; no studies in asthma or COPD.
- **Implication:** Theoretical benefit in exacerbations, but untested in patient populations.

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Preventive treatments – Vaccination

Vaccination

- **Influenza vaccine:** recommended for all asthma & COPD patients
- **No effective vaccines yet** for HRV
- **Challenges for HRV vaccine:**
  - 100 serotypes, including HRV-C → cross-reactivity difficult
- **Research directions:**
  - Conserved **VP0 capsid protein** → induced protective T-cell responses in mouse model.
  - **VP1 antibodies** may provide cross-serotype protection, but findings inconsistent.

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Thank you