Asthma

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Objectives

- Define asthma based on pathophysiology and spirometry including methacholine challenge.
- Describe the different stages of asthma severity (intermittent and persistent).
- Know the recommended treatments for each stage of asthma severity and describe the step-up and step-down approach to management.
- Describe the diagnosis and management strategy of asthma exacerbation.

QUESTION

A 22 year-old male is seen for evaluation of cough. He does not smoke and does not take regular medications. He states that he has been coughing daily for the past year, especially when he is exposed to strong odors. Two months ago, he started working in an auto body repair and paint shop. He states that he does not wear respiratory protection because he feels it makes his face too warm. His cough is worse at work.

Spirometry reveals an FEV1/FVC ratio of 0.64. Post bronchodilator FEV1 is only increased by 9%. Provocative concentration of methacholine causing 20% (PC_{20}) drop in FEV1 occurs at 1mg/mL. At 4 week follow-up he states he is no longer working and his cough and methacholine PC_{20} are unchanged.

Which of the following is the most likely diagnosis?

A. Cough Variant Asthma
B. Occupational Asthma
C. Reactive Airway Dysfunction Syndrome
D. Chronic Bronchitis

ASTHMA DEFINITION

- Diagnosis is clinical
- Hallmark symptoms:
  - Cough
  - Expiratory Wheeze
  - Dyspnea
- Exposure/Trigger mediated
  - Exercise, Allergen, Polutant, Fume, Weather, Irritant, Ect
- Physical Exam findings of atopia
  - Cobble stoning, nasal polyps, atopic dermatitis

Objectional Data

- Spirometry
  - Spirometry is variable (can be normal)
  - Typically Obstructive physiology (FEV/FVC<0.7)
  - Typically Bronchodilator responsive (FVC and/or FEV1 improvement > 200cc and 12%)
- Provocative Methacholine Challenge
  - PC_{20} at 8mg/mL or less
- Other Provocative Challenge Testing
  - Histamine, Mannitol, Exercise, Eucapnic voluntary Hyperventilation
- Exhaled Nitric Oxide (eNO)
  - Remains controversial
  - <25ppm considered negative, >50ppm considered positive for eosinophilic airway inflammation
  - Lowered by smoking, increased by Nitrate rich diet

What is asthma?

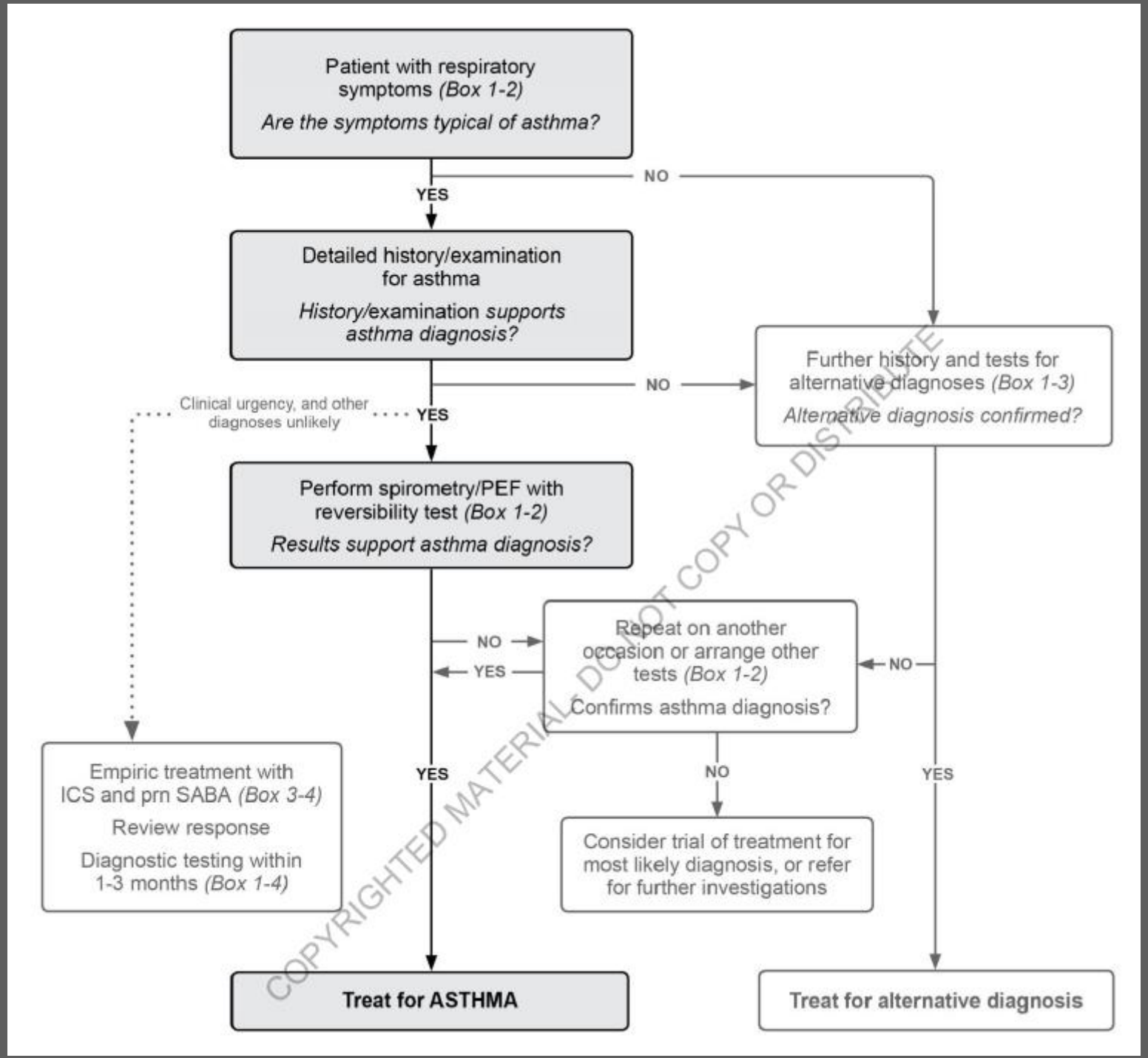
Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Airflow limitation may later become persistent.

Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'; however, these do not correlate strongly with specific pathological processes or treatment responses.

- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.

How is asthma diagnosed?

- The diagnosis of asthma is based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Test before treating, wherever possible, i.e. document the evidence for the diagnosis of asthma before starting controller treatment, as it is often more difficult to confirm the diagnosis afterwards.
- Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment, the elderly, and those in low-resource settings.


Patient with respiratory symptoms (Box 1-2)
Are the symptoms typical of asthma?
NO
YES
Detailed history/examination for asthma
History/examination supports asthma diagnosis?
NO
Further history and tests for alternative diagnoses (Box 1-3)
Alternative diagnosis confirmed?
Clinical urgency, and other diagnoses unlikely
YES
Perform spirometry/PEF with reversibility test (Box 1-2)
Results support asthma diagnosis?
NO
YES
Repeat on another occasion or arrange other tests (Box 1-2)
Confirms asthma diagnosis?
NO
Empiric treatment with ICS and prn SABA (Box 3-4)
Review response
Diagnostic testing within 1-3 months (Box 1-4)
YES
NO
YES
Consider trial of treatment for most likely diagnosis, or refer for further investigations
Treat for ASTHMA
Treat for alternative diagnosis
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ASTHMA MIMICS

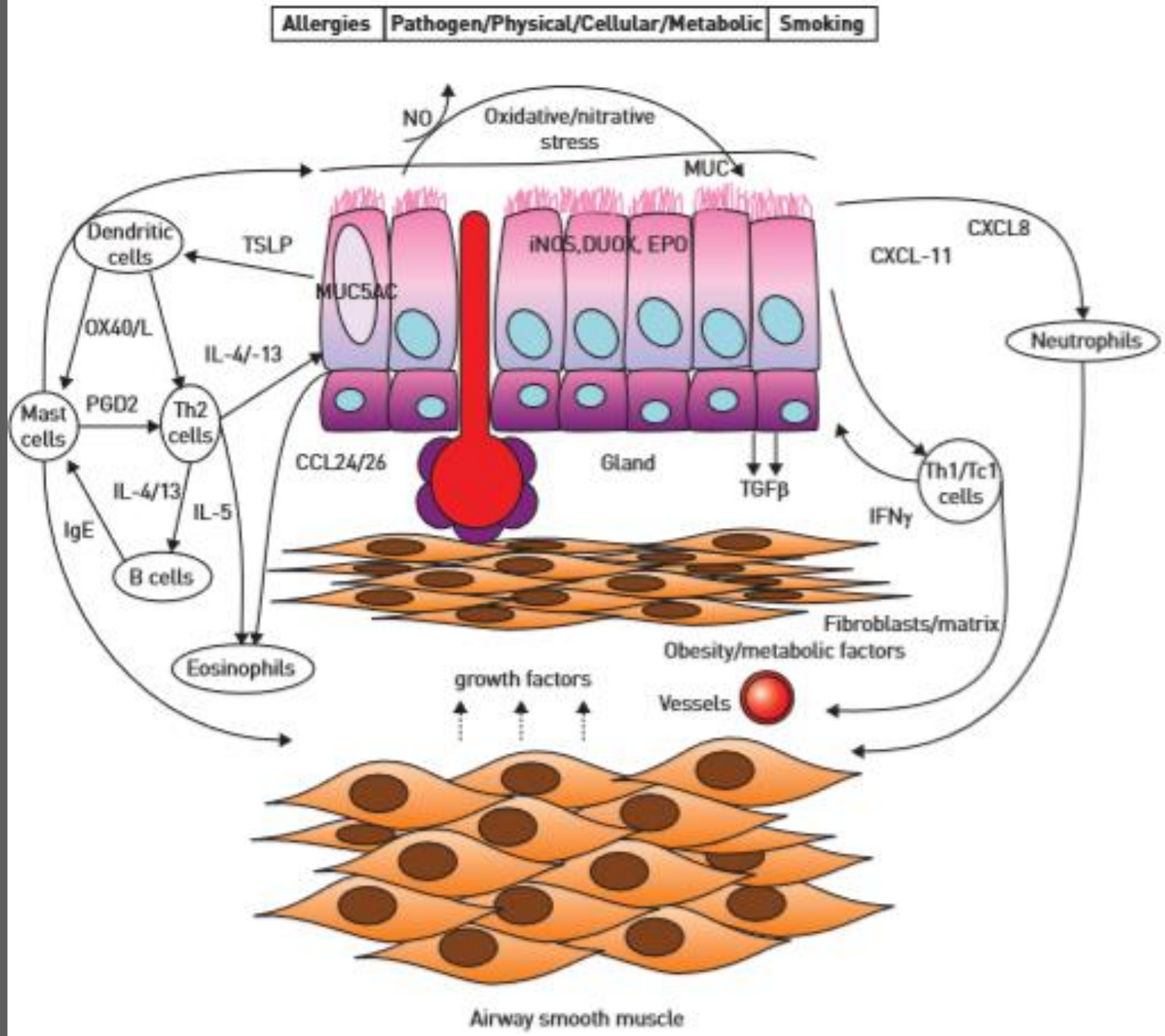
- Cystic Fibrosis
- Heart Failure
- Non-CF Bronchiectasis
- Inhaled Foreign body
- Vocal Cord Dysfunction
- COPD
- Medication related Cough
- Other Chronic Cough Syndromes (GERD, PND, ect)
- Reactive Airway Dysfunction Syndrome
- Interstitial Lung Disease
- Occupational Asthma
- Pulmonary Hypertension
- Bronchiolitis Obliterans
- Eosinophilic Granulomatosis with Polyangiitis
- Chronic Eosinophilic Pneumonia

QUESTION

A 64-year old man with asthma comes for an office visit. He reports daily cough, chest tightness, and dyspnea. He reports good compliance with montelukast and inhaled high-dose fluticasone/salmeterol and his inhaler technique is adequate. He still uses albuterol every day. He has no pets at home. He is allergic to house dust mites, cats, and dogs. Additionally he reports a long history of general "allergies" and endorses seasonal pollen as a frequent asthma trigger. He reports no reflux or sleep apnea symptoms. On physical you notice infraorbital edema and nasal turbinate pallor. Rhinorrhea is clear. There is a hyperplastic pattern of posterior pharynx.

What is the next best step for this patient?

A. Check an IgE level
B. Start Omalizumab
C. Change Albuterol to Levalbuterol
D. Start Tiotropium


Allergies
Pathogen/Physical/Cellular/Metabolic
Smoking
NO
Oxidative/nitrative stress
MUC
Dendritic cells
TSLP
MUC5AC
iNOS,DUOX, EPO
CXCL8
CXCL-11
Neutrophils
OX40/L
IL-4/-13
Mast cells
PGD2
Th2 cells
CCL24/26
Gland
TGFβ
Th1/Tc1 cells
IFNγ
IL-4/13
IL-5
IgE
B cells
Fibroblasts/matrix
Obesity/metabolic factors
Eosinophils
growth factors
Vessels
Airway smooth muscle

DISEASE SUSCEPTIBILITY

Genetic

- Interleukin Polymorphisms
- TH2 cell receptors
- Major Histocompatibility Complex
- Mast Cell Sensitivity

Epigenetic

- Environment
  - Pollutants
  - Tobacco
  - Allergens
- Obesity
- GERD

DISEASE PHENOTYPE

Allergic

- Eosinophilic
- TH2 Mediated
  - Eosinophils
  - Mast Cells
  - IL 4/5/13
- Associated with Atopy

Non-Allergic

- Neutrophilic
- TH1 Mediated
  - Fibroblasts
  - Interferon-γ
- Associated with Obesity

QUESTION

A 43- year-old man with adult onset asthma and allergic rhinitis is referred for uncontrolled asthma. He reports daily wheezing and night time awakenings at 1-2x per week. Spirometry in the office reveals an FEV1 of 70% and FEV1/FVC ratio of 65%. He is currently just on as needed albuterol which he is using daily. He asks if there is anything additionally that can help as his symptoms are now affecting his ability to perform his job as a laborer in a warehouse.

What is this patient's asthma severity classification?

A. Intermittent
B. Mild Persistent
C. Moderate Persistent
D. Severe Persistent

Classifying asthma severity and initiating treatment in youths greater than or equal to 12 years of age and adults

Components of severity		Classification of asthma severity (≥12 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8 to 19 years 85 percent 20 to 39 years 80 percent 40 to 59 years 75 percent 60 to 80 years 70 percent	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3 to 4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80 percent predicted • FEV_1/FVC normal	• FEV_1 ≥80 percent predicted • FEV_1/FVC normal	• FEV_1 >60 but <80 percent predicted • FEV_1/FVC reduced 5 percent	• FEV_1 <60 percent predicted • FEV_1/FVC reduced >5 percent
Risk	**Exacerbations requiring oral systemic glucocorticoids**	**0 to 1/year (see footnote)**	**≥2/year (see footnote)**		
		Consider severity and interval since last exacerbation			
		Frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			
Recommended step for initiating treatment		Step 1	Step 2	Step 3	Step 4 or 5
				And consider short course of oral systemic glucocorticoids	
		In two to six weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

QUESTION

The patient from the previous question asks if there is anything additionally that can help as his symptoms are now affecting his ability to perform his job as a laborer in a warehouse.

What is the best therapy regimen for this patient?

A. Continue albuterol and check inhaler technique
B. Add Budesonide/Formoterol 80/4.5
C. Add Tiotroprium
D. Add Montelukast

QUESTION

The patient from the previous question is started on Symbicort 80/4.5. He returns to the office at 6 months. He reports his last asthma symptoms were 4 months ago. He denies any night time awakenings. He hasn't used his short acting inhaler except for before exercise for prevention of symptoms. Repeat Spirometry in the office reveals an FEV1 of 96% without bronchodilator response and FEV1/FVC ratio of 87%.

What is the next best step?

A. Increase Symbicort dose to 160/4.5
B. Continue current therapy
C. Consider discontinuing his LABA
D. Add Montelukast

ASTHMA TOOLBOX

- Phosphodiesterase Inhibitors
  - Theophylline, Aminophylline
- Leukotriene Inhibitors
  - Montelukast, Zafirlukast, Zileuton
- Short Acting Beta Agonist (SABA)
  - Albuterol, levalbuterol, Terbutaline
- Long Acting Muscarinic Antagonists (LAMA)
  - Tiotropium Bromide
- Long Acting Beta Agonists (LABA)
  - Formoterol, Salmeterol
- Inhaled Corticosteroids (ICS)
  - Budesonide, Fluticasone, mometasone
- Glucocorticoids
- Biologics
  - IgE, IL-5, IL4/IL13

Intermittent asthma	**Persistent asthma: daily medication** Consult with asthma subspecialist if step 4 care or higher is required. Consider consultation at step 3.

Step 1

Preferred: Inhaled SABA, as needed

Step 2

Preferred: Low-dose ICS

Alternative*: Cromolyn, LTRA, or theophylline

Step 3

Preferred: Low-dose ICS plus LABA

or

Medium-dose ICS

Alternative*: Low-dose ICS *plus* LTRA, theophylline, or zileuton (Zyflo)

Step 4

Preferred: Medium-dose ICS plus LABA

Alternative*: Medium-dose ICS *plus* LTRA, theophylline, or zileuton

Step 5

Preferred: High-dose ICS plus LABA

Consider omalizumab (Xolair)† for patients who have allergies

Step 6‡

Preferred: High-dose ICS plus LABA plus oral systemic corticosteroid

Consider omalizumab† for patients who have allergies

AT EVERY VISIT

- Reassess control
- Assess patient medication adherence and technique
- Determine appropriateness for therapy step down or step up.
- Review/Modify Asthma Action Plan

QUESTION

29-year-old male with a history of childhood asthma presents for evaluation of asthma. He has persistent daily cough and shortness of breath. He notes symptoms are worse at night and in the morning. He's had 3 exacerbations in the past 12 months. He is currently on Formoterol/budesonide 160/4.5 and as needed albuterol. His symptoms are unchanged at home and at work. He is unable to identify any triggers. Physical is unremarkable except for bilateral wheezing. IgE and Eosinophil counts are normal.

In addition to evaluating inhaler technique, which of the following is most appropriate?

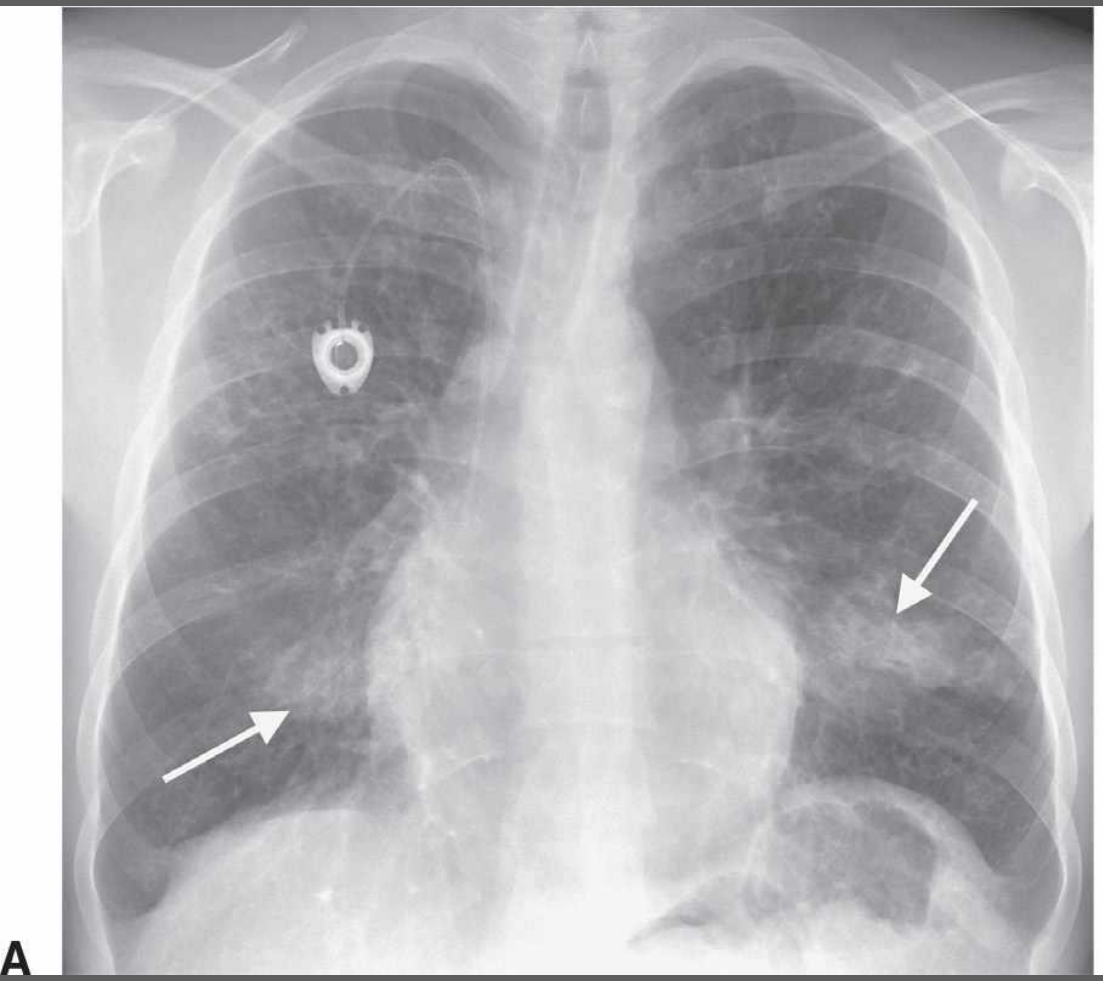
A. GERD evaluation
B. Prednisone for ABPA
C. Cardiopulmonary Exercise Testing
D. CT Chest

QUESTION

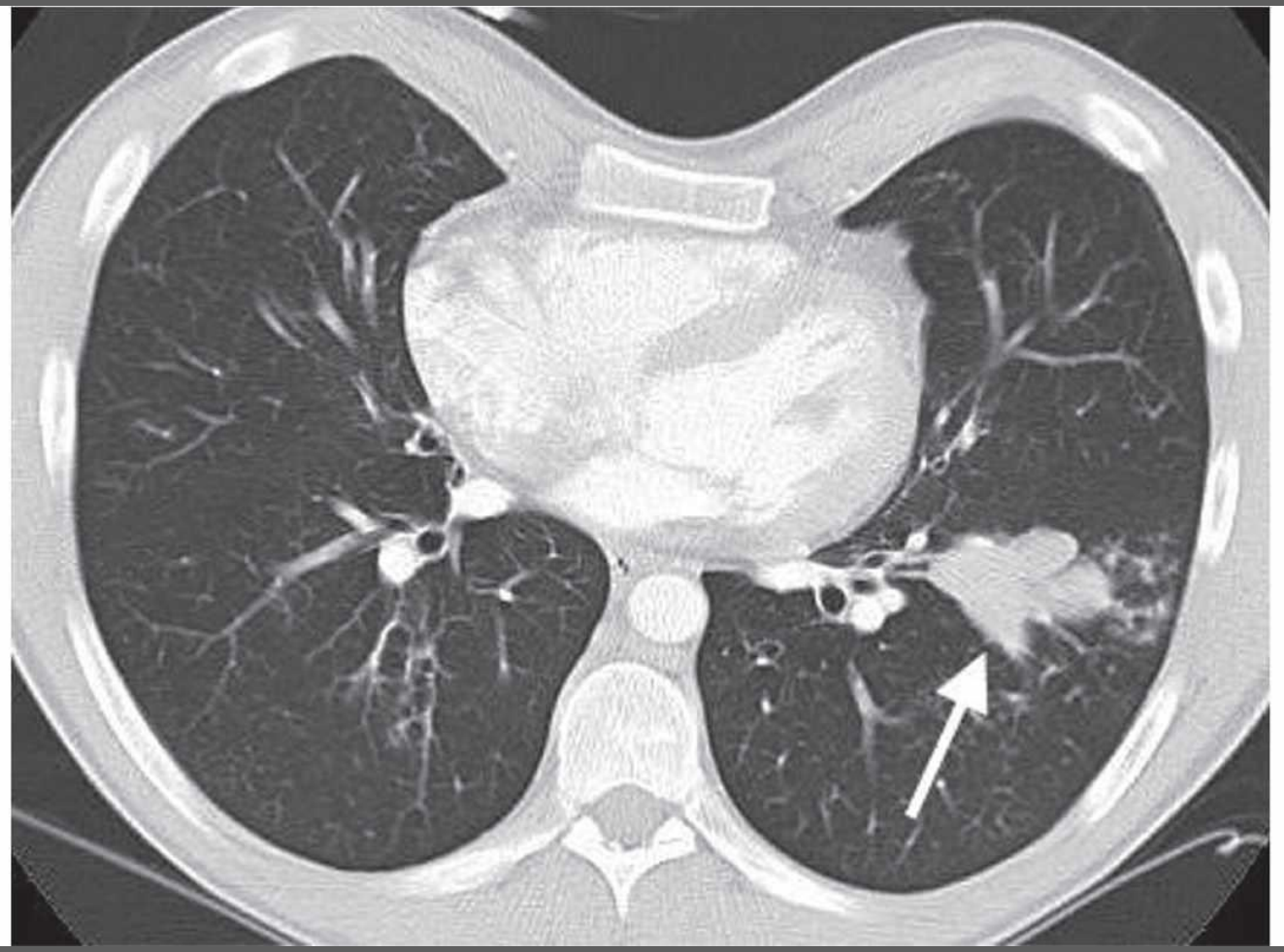
The patient from the Previous scenario has a has a negative GERD workup. Despite 3 months of PPI therapy symptoms are persistent. Repeat CBC is drawn which reveals a WBC count of 10,000 with 12% eosinophils and an IgE level of >1000. On CXR there is an opacity which the radiologist describes as having a "finger in glove" appearance.

Which of the following should be considered?

A. Coccidioidomycosis
B. Allergic Bronchopulmonary Aspergillosis (ABPA)
C. Nontuberculous Mycobacterial Pneumonia
D. Pulmonary Strongyloidiasis



A



B

ASTHMA COMORBIDITIES AND CONTRIBUTORY FACTORS

- Rhinosinusitis/nasal polyps
- ABPA
- Anxiety/depression
- Vocal cord dysfunction
- Obesity
- Smoking
- Obstructive sleep apnea
- Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
- Gastro-oesophageal reflux disease
- Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), b-adrenergic blockers, angiotensinconverting enzyme inhibitors

QUESTION

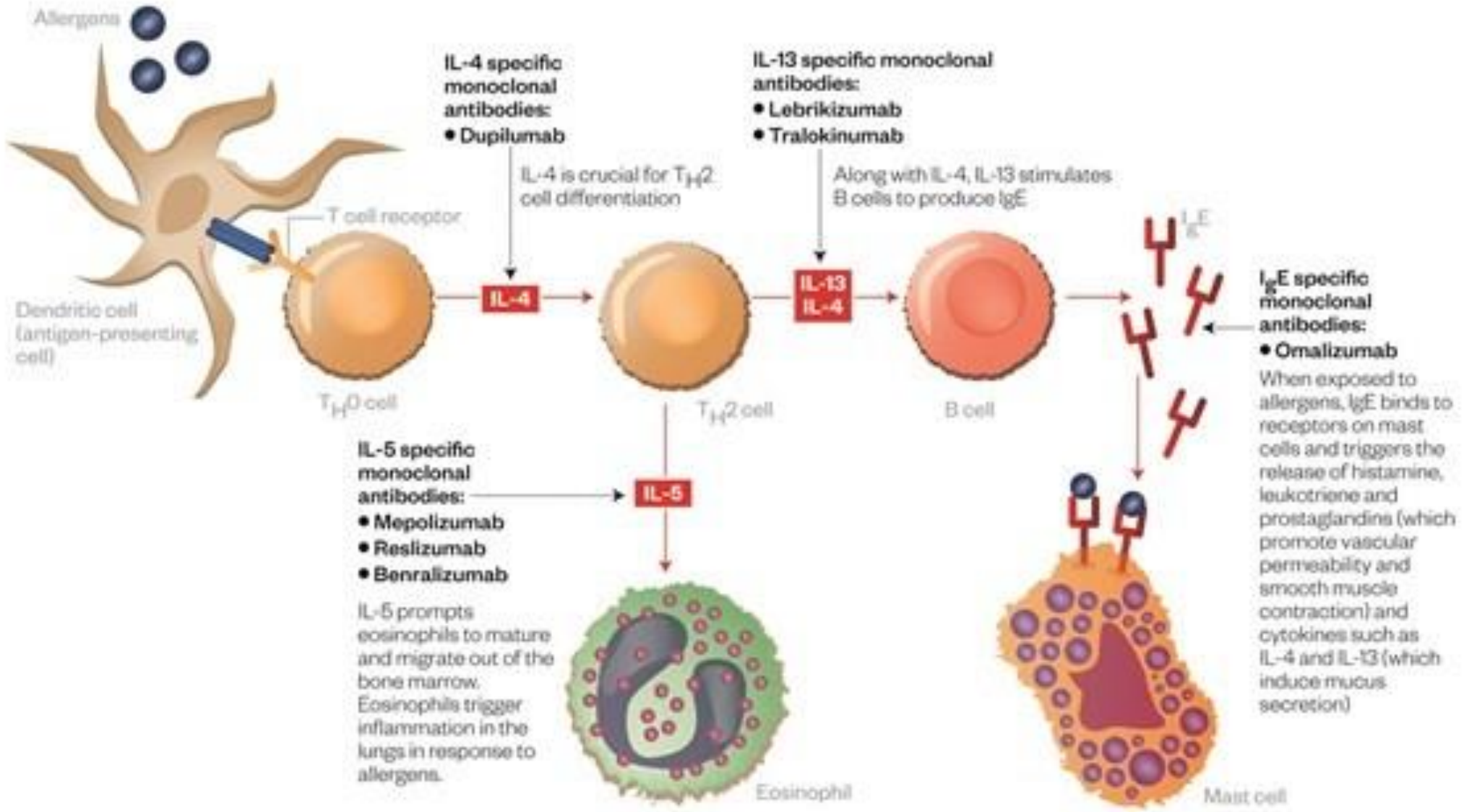
The Patient from the previous question is given a diagnosis of allergic bronchopulmonary aspergillosis. He is started on prednisone therapy. However, his symptoms remain uncontrolled.

Which of the following therapies could additionally be considered in this patient?

A. Itraconazole
B. Omalizumab
C. Bronchothermoplasy
D. Both A and B
E. All of the above

Targets for current and pipeline biologics

The discovery that asthma is a heterogeneous disease has paved the way for new, targeted biologic therapies. Omalizumab, which targets immunoglobulin E (I_gE), was the first to be approved over a decade ago and at least six biologics that target interleukins have now reached human trials.



Characteristics of Biologic Therapies for T2 High Asthma					
	Omalizumab	**Dupilumab**	**Benralizumab**	**Mepolizumab**	**Reslizumab**
FDA approval status	Approved, ≥6 years of age	Pending	Approved, ≥12 years of age	Approved, ≥12 years of age	Approved, ≥18 years of age
Mechanism of action	Binds to IgE (at Fcε3), which prevents IgE binding to the FcεR1 receptor on mast cells, basophils, dendritic cells and other key inflammatory cells.	Binds to IL-4Rα, which inhibits both IL-4 and IL-13 signaling.	Binds to the IL-5Ra on eosinophils and basophils leading to antibody-dependent cell-mediated cytotoxicity of these cells.	Binds to IL-5	Binds to IL-5
Route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous
Frequency	Every 2 to 4 weeks	Every two weeks	Every 4 weeks for the first three doses then every 8 weeks	Every four weeks	Every four weeks
Dose	Based on IgE and body weight (~0.016 mg/kg/IU/mL)	Likely 300 mg (fixed)	30 mg (fixed), pre-filled syringes	100 mg (fixed)	3.0 mg/kg (weight-based)
Biomarkers	Efficacy better with elevated eosinophils or FeNO	Efficacy better with elevated eosinophils or FeNO	Blood eosinophils ≥ 300 cells/μL	Blood eosinophils ≥ 150 cells/μL at initiation OR ≥ 300 cells/μL within the previous year	Blood eosinophils ≥ 400 cells/μL
Reduction in asthma exacerbations	Yes	Yes	Yes	Yes	Yes
Improvements in pulmonary functions	Minimal or mixed effect	Yes	Yes	Yes, especially in patients with very elevated eosinophil levels	Yes
Asthma symptom score and quality of life improvements vs placebo	Yes	Yes in Phase 2b study	Varied	Varied	Varied
Corticosteroid sparing effect	Data mixed	Not published	Yes	Yes	Data mixed

QUESTION

A 45-year old man with a 20-year-history of increasingly difficult to control asthma is seen in the clinic for ongoing wheezing and shortness of breath. His current regimen includes Budesonide/formoterol inhaler and an as needed albuterol inhaler. He is counseled on his inhaler technique and given an asthma action plan.

What is the cornerstone of the asthma action plan?

A. Short Acting Inhaler Frequency
B. Oxygen Saturation
C. Hospital Readmissions
D. Peak Expiratory Flow Rate

My Asthma Action Plan

Age ≥5 years

Patient Name: _____

Medical Record #: _____

Clinician's Name: _____ DOB: _____

Clinician's Phone #: _____ Completed by: _____ Date: _____

Long-Term Control Medicines	How Much To Take	How Often	Other Instructions
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
		_____ times per day EVERY DAY!	
Quick-Relief Medicines	**How Much To Take**	**How Often**	**Other Instructions**
		Take ONLY as needed	NOTE: If this medicine is needed frequently, call clinician to consider increasing long-term control medications.

Special instructions when I feel *good*, *not good*, and *awful*.

GREEN ZONE

I feel *good*.

{My peak flow is in the GREEN zone.}

My Personal Best Peak Flow

PREVENT asthma symptoms everyday:

- ☐ Take my long-term control medicines (above) every day.
- ☐ Before exercise, take _____ puffs of _____
- ☐ Avoid things that make my asthma worse like: _____

YELLOW ZONE

I do *not* feel *good*.

{My peak flow is in the YELLOW zone.}

My symptoms may include one or more of the following:

- Wheeze
- Tight chest
- Cough
- Shortness of breath
- Waking up at night with asthma symptoms
- Decreased ability to do usual activities
- _____

80% Personal Best

CAUTION. I should continue taking my long-term control asthma medicines every day AND:

- ☐ Take _____

If I still do not feel good, or my peak flow is not back in the *Green Zone* within one hour, then I should:

- ☐ Increase _____
- ☐ Add _____
- ☐ Call _____

RED ZONE

I feel *awful*.

{My peak flow is in the RED zone.}

Warning signs may include one or more of the following:

- It is getting harder and harder to breathe
- Unable to sleep or do usual activities because of trouble breathing

50% Personal Best

Unable

Peak Flow Meter

MEDICAL ALERT! Get help!

- ☐ Take _____ until I get help immediately.
- ☐ Take _____
- ☐ Call _____

Danger! Get help immediately! Call 9-1-1 if you have trouble walking or talking due to shortness of breath or lips or fingernails are gray or blue.

QUESTION

A 27-year-old is brought to the ED in respiratory distress by her coworkers. She has a long history of asthma that is usually minimally symptomatic but has been punctuated by the sudden development of severe attacks requiring intubation on four prior occasions.

On arrival at the ED, she is in too much distress to provide additional history. Her coworker sites that she complained of throat tightness, marked dyspnea, and wheezing.

She is tachypneic at 32 BPM and using accessory muscles. HR is 120. Saturation is 90% on 50% face mask.

Which of the following is the best next step?

A. Peak Expiratory flow
B. Transition to Noninvasive mask
C. Aminophylline infusion
D. Arterial Blood Gas

ASTHMA EXACERBATION

- Increase in baseline
  - Dyspnea
  - Cough
  - Wheezing or Chest Tightness
- Decrease in lung Function (FEV1/PEF)

- Common Triggers
  - Viral infection
  - Allergen Exposure
  - Air Quality
  - Poor Medication Adherence
  - Seasonal Changes

OUTPATIENT ASTHMA EXACERBATION

- Dictated clearly by Asthma Action Plan
- Management different depending on baseline asthma severity level
- Clear escalation instructions given
- PRN prescriptions written before hand

- SABA PRN
  - Increase SABA frequency (at least 20 minutes apart)
  - Introduce PRN LABA/ICS
  - Max formoterol dose (72mcg)
- ICS/LABA
  - Increase SABA frequency
  - Increase LABA/ICS frequency
- All of the Above
  - OCS typically 40-50mg for 5-7 days
  - Emergency Room assessment if symptoms
    - Longer than 2-3 days
    - PEF<50-60% baseline

HOSPITALIZATION

- Mild Exacerbation:
  - PEF>40%
  - SpO2>90%
  - Sustained good response with SVN/SABA (PEF>70% for 60 minutes)
  - Expectant management at home
- Moderate Exacerbation:
  - PEF<40%
  - SpO2>90%
  - Incomplete response with SVN/SABA (PEF 40-80%)
  - Hospital Ward
- Severe Exacerbation:
  - PEF<40%
  - SpO2<90%
  - Poor response with SVN/SABA (PEF <40%)
  - Severe Symptoms (accessory muscle use, retractions, ect)
  - Hypercarbia (CO>42)
  - Consider MICU and adjunctive therapy

THERAPY

- Inhaled Short Acting Beta Agonist
- Ipratroprium Bromide
- Controlled Oxygen Therapy (SpO_2 93-95%)
- Can continue ICS
- Systemic Corticosteroids (5-7 day course equivalent to 10-14 days)
  - No taper necessary
- Antibiotics not recommended (unless evidence of infection)

Ann Thorac Med. 2014 Oct-Dec; 9(4): 187–192.
doi: 10.4103/1817-1737.140120
PMCID: PMC4166064
PMID: 25276236

Corticosteroids in the treatment of acute asthma

Abdullah A. Alangari

- No significant difference between IV and PO steroids
- No significant difference between low dose (2mg/kg/day or 80mg/day) versus higher doses

QUESTION

The patient from the previous question appears more somnolent. You decide to obtain an arterial blood gas with the following results:

pH 7.24

CO2 60

PO2 55

HCO2 24

FiO2 50%

Which of the following is the best next step?

A. Intubation
B. Bipap Mask
C. Continuous SVN and Repeat ABG in 20 minutes
D. CT Head

QUESTION

The patient from the previous question is intubated and sedated.

Which of the following is the most appropriate ventilator strategy?

A. R 30 Vt 400 F 50L/min
B. R 30 Vt 400 F 90L/min
C. R 20 Vt 400 F 50L/min
D. R 20 Vt 400 F 90L/min

ADJUNCTS

- Non-invasive positive pressure ventilation
- Magnesium (2g over 20 minutes)
- Continuous Nebulization
- Intubation (Ketamine induction)
- Neuromuscular Blockade (vecuronium or Cisatracurium infusion)
- IM Epinephrine (if evidence of anaphylaxis present)

Questions?

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