Allergy and Immunology Board Review Corner: 2018

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FIT Board Review Corner – January 2018

Welcome to the FIT Board Review Corner, prepared by Amar Dixit, MD and Christin Deal, MD, senior and junior representatives of ACAAI’s Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Middleton’s Allergy Principles and Practice, 8th Edition
N. Franklin Adkinson Jr., MD, Bruce S Bochner, MD, A Wesley Burks, MD, William W Busse, MD, Stephen T Holgate, MD, DSc, FMedSci, Robert F Lemanske, Jr., MD and Robyn E O’Hehir, FRACP, PhD, FRCPath

Chapter 44 (pages 700-711): Development, Structure, and Physiology in Normal Lung and Asthma
Prepared by: Amar Dixit, MD

1. What is the test of choice to monitor a patient’s asthma status?
   a. Exhaled Nitric Oxide
   b. Spirometry
   c. Full Pulmonary Function Testing
   d. Patient’s clinical history and presentation

2. What is the test of choice to appropriately measure a patient’s total lung capacity, functional reserve capacity, and residual volume?
   a. Spirometry
   b. CT scan without contrast of the chest
   c. Helium Dilution Technique
   d. Body Plethysmography

3. Which of the following lung volume measurements would be expected to first become abnormal in asthma?
   a. Residual Volume
   b. Total Lung Capacity
   c. Vital Capacity
   d. Expiratory Reserve Volume

4. For spirometry results to be considered reproducible, what is the maximum volume error?
   a. 50 mL
   b. 100 mL
   c. 150 mL
   d. 200 mL
5. What volume amount and percent change in pre-bronchodilator FEV1 or FVC to post-
bronchodilator FEV1 or FVC, respectively, are considered to be a positive bronchodilator
response?
   a. 150 mL and 10%
   b. 150 mL and 12%
   c. 200 mL and 12%
   d. 200 mL and 15%

6. In a patient with lung disease, an elevated DLCO indicates which of following disease states?
   a. COPD
   b. Interstitial Lung Disease
   c. Uncontrolled asthma
   d. Well controlled asthma

7. What is the difference between male and female gender in terms of airway/lung volume ratios
   prior to puberty?
   a. Females have a greater airway/lung volume ratio than males
   b. Males have a greater airway/lung volume ratio than females
   c. No difference
   d. Not well studied

8. What is the most typical change seen on the inspiratory flow loop in vocal cord dysfunction?
   a. No change seen
   b. Consistent truncation of the inspiratory flow loop
   c. Partial truncation of the inspiratory flow loop
   d. Enlargement of the inspiratory flow loop

9. Which of the following measurement is best to detect subtle airflow limitation?
   a. Peak expiratory flow
   b. FEV1
   c. FEF25-75
   d. FEV1/FVC

10. When does the embryonic stage of lung development begin and end?
    a. Begins at the 3rd or 4th week and ends at the 7th week of gestation
    b. Begins at the 15th week and ends at the 17th week of gestation
    c. Begins at the 16th week and ends at the 26th week of gestation
    d. Begins at the 24th week and ends at the 38th week of gestation
Answers

1. B, pg. 702
   Spirometry correlates well with airway cross-sectional area and is more sensitive than a patient’s report of symptoms and physical examination results. Spirometry can predict mortality for patients with chronic airway disease. Spirometry is the test of choice in all settings.

2. D, pg. 705
   Body plethysmography relies on Boyle’s law and gas compression. It may overestimate the true TLC, FRC, and RV, but will correctly diagnosis obstruction.

3. A, pg. 705 and 711
   Elevations in residual volume (>150%) are usually the first alteration in lung volume. The residual volume is a sensitive measure of the function of the small airways.

4. C, pg. 710
   It is critical that spirometry be reproducible. Successive spirometry results taken at one time with the same patient should not have greater than 150 mL in variation.

5. C, pg. 711
   ATS criteria states that FEV1 or FVC should increase by at least 200 mL and 12%.

6. C, pg. 711
   In patients with asthma the DLCO is either normal or elevated. If the DLCO is elevated that indicates that the asthma is uncontrolled. The DLCO would be decreased in COPD and interstitial lung disease.

7. A, pg. 700 and 701
   Males prior to puberty have a smaller airways than females and thus a smaller airway/lung volume ratio. This difference in airway size has been proposed as a theory to explain the increased prevalence of asthma among prepubertal males compare to females.

8. C, pg. 704
   Typically, partial truncation of the inspiratory flow loops is seen in vocal cord dysfunction thought vocal cord dysfunction can present with different patterns. A consistent truncation is generally indicative of a large airway obstruction or an extra thoracic lesion.

9. D, pg. 704
   FEV1/FVC is the test of choice. FEV1 is the most reproducible pulmonary function test, but can be normal in those with significant disease. FEF_{25-75} is determined over the middle 50% of the patient’s expired volume. It varies more and is less reproducible. It use in adults is discouraged.

10. A, pg. 700
    During the embryonic stage, the lung sacs develop from the ventral wall of the esophagus. This is the reason behind the common features of the lung and the gastrointestinal tract. The pseudoglandular stage occurs from the 15th to the 17th week of gestation. The canalicular stage occurs from the 16th week to the 26th week of gestation. The saccular period occurs from the 24th week to the 38th week of gestation.
FIT Board Review Corner – February 2018

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Chapter 48 (pages 754-766): Epidemiology of Asthma and Allergic Airway Diseases
Prepared by: Evelyn Lomasney, MD

1. Bronchial challenges are useful tests for the evaluation of asthma. Tests can be performed with direct acting constrictors or indirect-acting constrictors. Which of the following is an example of an indirect-acting constrictor?
   a. Histamine
   b. Methacholine
   c. Albuterol
   d. Mannitol

2. Currently there is no validated questionnaire for the diagnosis of food allergy. What is considered the gold-standard for the diagnosis of food allergy?
   a. Open food challenge
   b. Double-blinded placebo controlled food challenge
   c. Specific IgE testing
   d. Blinded food challenge

3. What was the estimated overall prevalence rate of asthma on the mainland USA in the 2010 Behavioral Risk Factor Surveillance System (BRFSS)?
   a. 3%
   b. 5%
   c. 8%
   d. 12%

4. Which study has best documented the world-wide prevalence of eczema?
   a. ISAAC Phase Three
   b. ISAAC Phase One
5. Multiple cross-sectional surveys from 1952 – 2002 have shown that the prevalence of asthma has increased at which of the following rates?
   a. Doubling every 7 years
   b. Doubling every 14 years
   c. Tripling every 10 years
   d. Tripling every 20 years

6. In skin prick testing, what is the wheal diameter below which the “positive result” should be discounted as irrelevant?
   a. 2 mm
   b. 3 mm
   c. 4 mm
   d. 5 mm

7. In the United States, the NHIS, a population-based interview survey of US households, is a key source of information of trends in asthma prevalence. In 2001, the survey question “Do you still have asthma” was added in order to assess which of the following?
   a. Lifetime prevalence
   b. Attack prevalence
   c. Incidence
   d. Current prevalence

8. According to NHIS data the current asthma prevalence rates among whites increased by 0.8% per annum. This was significantly different from the current asthma prevalence rates among blacks. What percentage did the asthma prevalence rates increase in the black population?
   a. 4%
   b. 6%
   c. 8%
   d. 10%

9. In the 2004 NHIS survey the prevalence of allergic rhinitis was the highest in which of the following regions of the United States?
   a. South
   b. Northeast
   c. West
   d. Midwest
10. Hospital admissions for “dermatitis due to food” in England and Wales increased from 5 cases per million in 1990 to 26 cases per million in 2004, an increase of 13% per annum. Critics have questioned whether this represents a true increase in food allergy prevalence. What is one alternative explanation?
   a. Increased access to health care
   b. Changes in coding behavior of physicians
   c. Increased food allergy testing
   d. Increase in peanut specific food allergy rates
Answers

1. D, pg.757
Both methacholine and histamine are considered direct-acting constrictors in bronchial challenges. Indirect acting constrictors include mannitol, adenosine, exercise, and cold air. There is little difference between the use of histamine and methacholine; however, methacholine is used more widely due to fewer side effects. One disadvantage of the direct acting constrictors is that they produce positive tests for patients with asthma and COPD. This has led to the use of alternative agents that act indirectly by releasing mediators from mast cells in the airway. However, the indirect acting constrictors have not been studied as extensively as methacholine and histamine.

2. B, pg. 758
The gold standard for diagnosing food allergy is the double-blinded placebo controlled food challenge. Currently there are no validated questionnaires for the diagnosis for food allergy, unlike other allergic conditions. This has complicated the epidemiologic study of food allergy. Many reported food allergy symptoms are unable to be confirmed when a full diagnostic evaluation is completed. As such, estimates from invalidated questionnaires are likely to be inflated.

3. C, pg.760
The 2010 Behavioral Risk Factor Surveillance Systemic (BRFSS) estimated the overall current prevalence rate of asthma on mainland USA as 8.6%, ranging from 6% in Tennessee and 11.1% in Vermont. The definition of current asthma was defined as positive answers to two questions: Have you ever been told by a doctor, nurse or other health care professional that you had asthma? Do you still have asthma?

4. A, pg. 761
The world-wide prevalence of eczema was best documented in ISAAC Phase Three, in which the prevalence rates for 6- to 7- year old children ranged from 0.9% in India to 22.5% in Ecuador. The overall prevalence among 13- to 14- year old adolescents was 7.3%. The world wide prevalence of eczema has increased in most regions of the world, and has remained stable in only Western, Northern and Eastern Europe.

5. B, pg. 763
From the 1950s to the mid 1990’s the prevalence rates of asthma increased at doubling rate of every 14 years. This occurred regardless of the definition used and the initial prevalence rate. In the mid-1990s reports began to suggest that the rate of increase may be declining.

In skin prick testing, wheals less than 3 mm in diameter usually are discounted as irrelevant.
7. D, pg. 764
This question was added to the 2001 survey in order to assess current prevalence rates of asthma. In 2001, the overall current prevalence rate was 7.3%.

8. A, pg. 763-764
The current asthma prevalence rates among blacks increased by 4% per annum. Between 2001 and 2009, the prevalence rate of asthma among blacks increased from 8.4% to 11.9%. Disparities in prevalence rates among racial and ethnic groups likely represents differences in genetic, environmental, social and cultural influences.

9. C, pg. 765
The 2004 NHIS survey showed that the prevalence of allergic rhinitis in the United States was highest in the West (10.8%), followed by Northeast (9.5%), South (8%) and Midwest (7.2%). The overall prevalence of allergic rhinitis in the United States was 9%.

10. B, pg. 766
Changes in coding requirements and behavior of physicians as well as changes in awareness and behavior of patients have been cited as alternative explanations for the increase in these hospitalizations. Although food allergy prevalence may be increasing in the United States, the rates are much lower.
FIT Board Review Corner – March 2018

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Chapter 48 (pages 766-781): Epidemiology of Asthma and Allergic Airway Diseases
Prepared by: Tammy Peng, MD

1. In children with asthma, lower blood levels of which of the following nutrients has been associated with increased asthma severity, including increased IgE levels, eosinophilia, methacholine responsiveness, asthma-related hospitalization, asthma exacerbations, use of anti-inflammatory medication, use of oral corticosteroids, and reduced asthma control scores?
   A. Vitamin A
   B. Zinc
   C. Vitamin C
   D. Vitamin D

2. Levels of which nutrient have been found to directly correlate with increased bronchial responsiveness with histamine challenge?
   A. Magnesium
   B. Sodium
   C. Copper
   D. Zinc

3. The Wisconsin Childhood Origins of Asthma (COAST) study found that wheezing in the first year of life associated with a particular virus is the strongest predictor of wheezing in the third year of life. Which of the following is that virus?
   A. Human rhinovirus (HRV)
   B. Influenza
   C. RSV
   D. Enterovirus

4. Which HRV type has been implicated in most episodes of acute asthma requiring hospital attention?
   A. HRV-A
   B. HRV-B
   C. HRV-C
5. Which of the following describes the “healthy smoker effect?”
   A. Tendency for smokers to have nonspecific responsiveness of the airways
   B. Tendency for young smokers to have greater lung function and less underlying airway responsiveness
   C. Tendency for smokers to have wheezing that declines after cessation of smoking
   D. Tendency for smoking to narrow the baseline airway caliber in older people

6. Which of the following is an associated risk factor for allergic rhinitis?
   A. Parental history
   B. Young age
   C. Low socioeconomic status
   D. Vaginal delivery

7. Which of the following has been identified to be protective against the development of eczema?
   A. Early life exposure to endotoxin
   B. Male gender
   C. Breastfeeding
   D. Black and Asian race or ethnicity

8. In a U.S. cohort study by Gent and colleagues, among children using maintenance medication, the level of which of the following pollutants was significantly associated with worsening of respiratory symptoms and increase in rescue medication use?
   A. nitrogen dioxide
   B. sulfur dioxide
   C. ozone
   D. particulate matter

9. In a study by Bronniman and Burrows following 136 asthmatics in Tucson, Arizona over a 9 year period, which of the following was the strongest predictor of remission?
   A. less frequent wheezing
   B. normal percent predicted FEV₁ at baseline
   C. less frequent episodes of shortness of breath with wheezing
   D. chronic productive cough

10. Sensitization to which of the following indoor allergens has been linked to presence and persistence of asthma?
    A. house dust mite
    B. household pets
    C. mold
    D. foods
Answers:

1. Answer: D. Vitamin D pg.768

In children with asthma, lower blood levels of vitamin D have been associated with increased asthma severity, including increased IgE levels, eosinophilia, methacholine responsiveness, asthma-related hospitalization, asthma exacerbations, use of anti-inflammatory medication, use of oral corticosteroids, and reduced asthma control scores. Similar findings have been reported for adults with asthma. Lower serum 25-OH-D concentrations have been associated with increased severity of disease in children with atopic dermatitis. Please also reference Table 48-4 on p. 767 to review nutrients implicated in asthma as well as their activity and potential mechanisms of action.

2. Answer: B. Sodium pg. 767

Observational and randomized studies have directly correlated dietary sodium levels with increased bronchial responsiveness on histamine challenge. One study demonstrated this response in males but not females. One study found increased magnesium intake is associated with reduced risk for bronchial hyperresponsiveness and wheeze. Please also reference Table 48-4 to review nutrients implicated in asthma and their potential mechanisms of effect.

3. Answer: A. Human rhinovirus (HRV) pg. 770

The COAST study prospectively evaluated timing, frequency, severity and cause of symptomatic viral infection in the first 3 years of life in relation to later wheezing illness in a cohort of 289 neonates at high familial risk for asthma. This study highlighted the prognostic importance of HRV. Having one or more HRV-associated wheezing episodes during the first year of life was more strongly associated with wheezing in the third year than having one or more RSV-associated wheezing episodes in the first three years of life. Also, first-year wheezing associated with HRV was the strongest predictor for third-year wheeze.

4. Answer: C. HRV-C pg.771

In 2006, a novel HRV designated HRV-C was identified. It has been implicated in the natural history of wheezing disease and asthma with important prognostic significance. Studies in Australia as well as Hong Kong have isolated HRV-C in children hospitalized with acute asthma. HRV-C appears to be more virulent than other HRV serotypes, especially in children with atopic sensitization.

5. Answer: B. Tendency for young smokers to have greater lung function and less underlying airway responsiveness pg. 777

The healthy smoker effect is a phenomenon where young smokers tend to have somewhat greater lung function and less underlying airway responsiveness than nonsmokers, perhaps because of the sensitivity of asthmatic lung to cigarette smoke.

6. Answer: A. Parental history pg. 777
The most frequently cited risk factors of allergic rhinitis include increasing age, atopy and high socioeconomic status. Parental history is positively associated with development of allergic rhinitis in offspring. Younger gestational age at birth has been associated with decreased risk of allergic rhinitis. Some researchers have postulated early-life microbial exposure may modulate risk of allergic rhinitis. This hypothesis is supported by the observations that birth by caesarean section is a risk factor for allergic rhinitis.

7. Answer: A. Early life exposure to endotoxin pg. 778

Black and Asian race or ethnicity is a risk factor along with male gender for development of eczema. Early-life exposure to endotoxin appears to protect against the development of eczema, as reported in several studies. Neither breastfeeding nor timing of solid food introduction has been shown to be protective. There is some evidence that hydrolyzed infant formulas and supplementation with probiotics may afford some protection, but study results are mixed.

8. Answer: C. ozone pg. 774

Among children using maintenance medication, the level of ozone was significantly associated with worsening of respiratory symptoms and increase in rescue medication use. Significant associations were not found for children not using maintenance medication. Findings suggest that children with asthma using maintenance medication are particularly vulnerable to ozone, even after adjusting for exposure to particulate matter and at air pollution levels below EPA air quality standards.

9. Answer: B. normal percent predicted FEV$_1$ at baseline pg. 780

Patients were classified as in remission if they had active disease at baseline and at follow-up denied medication use, asthma attacks and frequent attacks of shortness of breath with wheezing during the preceding year. Remission was more common in those with less frequent wheezing, less frequent asthma attacks and less frequent attacks of shortness of breath with wheezing. Remission was significantly less likely in those with chronic productive cough or coexisting diagnosis of chronic bronchitis or emphysema. A normal level of percent predicated FEV$_1$ at baseline was the most powerful predictor of remission.

10. Answer: C. mold pg. 776

Sensitization to mold has been linked to presence, persistence and severity of asthma. A Finnish study observed that exposure to indoor molds increases severity of asthma and removing the source relieves or eliminates symptoms and signs of asthma. Not all studies support the hypothesis that allergen exposure causes asthma. One British cohort study did not find significant association between levels of house dust mite exposure and sensitization or wheeze. A German birth cohort study showed strong association between sensitivity to house dust mite allergens or cat allergens and wheezing from 3 years of age, but there was no association noted between early indoor allergen exposure and physician-diagnosed asthma or wheeze.
FIT Board Review Corner – April 2018

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Chapter 59 (pages 970-985): Occupational Allergy and Asthma
Prepared by: Kara Wada, MD

1. High molecular weight compounds are mostly protein or polysaccharides and act as complete antigens directly provoking an IgE-mediated response. Which of the following agents is a HMW agent?
   A. Isocyanates
   B. Metals
   C. Cereals
   D. Wood dusts

2. Which of the following agents is the most frequent and most often reported cause of occupational asthma in Western countries?
   A. Diisocyanates
   B. Acrylates
   C. Wood dust
   D. Baking products

3. What is the single most important risk factor for Occupational Asthma?
   A. Exposure
   B. Atopy
   C. Smoking
   D. Rhinconjunctivitis

4. What agent should you suspect in an automobile worker with occupational asthma who works in finish coating?
   A. TDI (toluene diisocyanate)
   B. HDI (hexamethylene diisocyanate)
   C. MDI (methylene diphenyl diisocyanate)
   D. LDI (lysine diisocyanate)

5. Patients with OA and exposure to which of the following agents would have the best prognosis?
   A. TDI (toluene diisocyanate)
   B. HDI (hexamethylene diisocyanate)
C. MDI (methylene diphenyl diisocynate)
D. LDI (lysine diisocyanate)

6. Which of the following conditions is characterized by the lack of a latency period and immunologic sensitization, and occurs after a single massive irritant exposure?
   A. Reactive airway dysfunction syndrome
   B. Work-related asthma
   C. Work-exacerbated asthma
   D. Acute respiratory distress syndrome

7. The epidemiology of occupational asthma is challenging. Which of the following statements is true?
   A. Data generated by voluntary notification schemes rely mainly on confirmatory concrete data.
   B. Medicolegal statistics from compensation boards may overestimate prevalence.
   C. Population surveys minimize survivor bias, but lack confirmatory testing data.
   D. Occupational rhinitis is known to be equally as common as occupational asthma.

8. Sputum eosinophils have been used as an objective measure of airway inflammation in occupational asthma. What is thought to be the ideal timeframe for sputum collection to check for sputum eosinophils?
   A. 1 hour post exposure
   B. 7-24 hours post exposure
   C. 3-5 days post exposure
   D. 7-10 days post exposure

9. Exposure to which product is associated with work-related anaphylaxis in people who work in nail salons?
   A. Latex
   B. Terachlorophtalic acids
   C. Aldehydes
   D. Methacrylates

10. Occupational asthma related to western red cedar is due to exposure to which of the following?
    A. Plicatic acid
    B. Bromelain
    C. Trimellitic acid
    D. Carmine

Answers:
1. C.
   Cereals

2. D
   Baking products are the leading cause of OA in most Western countries with 0.8-2.4 cases per 1000 exposed workers and a cumulative incidence rate of 12.4% for IgE mediated sensitization to bakery allergens, 8.4% for OR and 6.1% for OA.
   Middleton’s 8th edition, Page 981
3. A.
The intensity of exposure to sensitizing agents is currently the most well-characterized and most important environmental risk factor for the development of OA.
Middleton’s 8th edition, Page 974, Table 59-4

4. B
Hexamethylene diisocyanate (HDI) as it is used extensively in spray paints.
Middleton’s 8th edition, Page 982

5. B
OA due to HDI seems to carry a better prognosis than OA due to TDI and MDI.
Middleton’s 8th edition, Page 983

6. A
Reactive airways dysfunction syndrome refers to a type of OA without latency and immunologic sensitization, occurring after a single massive irritant exposure with consequent severe airway injury, and resulting in persistent airway inflammation and nonspecific bronchial hyperresponsiveness.
Middleton’s 8th edition, Page 970

7. C
Data generated by voluntary notification schemes rely on the physician’s diagnostic opinion and no confirmatory tests are required. Medicolegal statistics may underestimate the true incidence of OA because not everyone applies for compensation. Population surveys minimize survivor bias, but are limited by the lack of confirmation testing. OR is 2-4 times more common than OA.
Middleton’s 8th edition, Page 972

8. B
The best timing for the collection of induced sputum with respect to exposure to occupational agents is likely to be 7-24 hours after exposure.
Middleton’s 8th edition, Page 979

9. D
The answer is methacrylates.
Middleton’s 8th edition, Page 978 and table 59-2 on page 973

10. A
Plicatic acid is present in western red cedar and in small amounts in eastern white cedar. Plicatic acid has been shown to induce specific bronchial reactions on bronchial challenge testing in exposed workers with a history compatible with OA.
Middleton’s 8th edition, Page 983
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Chapter 60 (pages 986-99): Pathology of Asthma
Prepared by: Shahab Virani, MD and Kathleen Lee-Sarwar, MD

1. What is the name for the eosinophil breakdown products that may be visible by microscopy in the mucus of asthmatic patients?

   A. Calcium oxalate crystals
   B. Charcot-Leyden crystals
   C. Curschmann crystals
   D. Birbeck granules

2. What is the name for the distinctive spiral formations that may be found on microscopy in the mucus of asthmatic patients?

   A. Döhle bodies
   B. Charcot-Leyden spirals
   C. Curschmann spirals
   D. Azurophilic granules

3. A 30 year-old female presents as a new patient to Allergy and Immunology clinic. She reports a history of cough, chest tightness, and wheezing that worsens when she exercises, has an upper respiratory infection, and is around cats. She wakes up at night with these symptoms approximately three times per week. She was prescribed an albuterol inhaler by her primary care physician and reports that her symptoms are relieved by its use, but she does feel the need to use it more days than not. Spirometry reveals FEV1 68% predicted. A sputum sample is obtained and exhaled fraction of nitric oxide is measured.

Which of the following clinical findings suggests that she would be likely to respond well to treatment with corticosteroids?
A. Elevated exhaled fraction of nitric oxide  
B. Abundant sputum neutrophils  
C. FEV1 less than 80% predicted  
D. Few or no sputum eosinophils

4. Corticosteroids have which of the following effects?
   A. Inhibit eosinophil apoptosis  
   B. Inhibit neutrophil apoptosis  
   C. Promote neutrophil apoptosis  
   D. Trigger mast cell degranulation

5. Mary and Laura are sisters coming to clinic for follow-up of asthma. Mary reports one asthma exacerbation in the last year in the setting of a cold and was able to control her asthma symptoms with the use of an inhaled corticosteroid in addition to as-needed use of inhaled albuterol. Laura has had frequent exacerbations triggered by a variety of exposures including weather changes and upper respiratory infections. She has required six courses of systemic steroids in the past year. She reports using her albuterol inhaler at least once every day, and is waking up from sleep with a cough and chest tightness four times weekly.

Which of the following pathologic findings would you expect to be exhibited by Laura, but not by Mary?

   A. Bronchial goblet cell hyperplasia  
   B. Increased airway mucosal vascularity  
   C. Thickening of the reticular basement membrane  
   D. Increased alveolar tissue mast cell numbers

6. At what point in the natural history of asthma can pathologic evidence of remodeling be found?
   A. After at least three acute asthma exacerbations  
   B. Only during acute asthma exacerbations  
   C. Within a few years of disease onset  
   D. Starting approximately twenty years after diagnosis

7. Which of the following is a chemoattractant that attracts eosinophils to the airway mucosa in asthma?
   A. CCL2  
   B. CXCL5  
   C. CXCL7  
   D. CXCL8
8. Which of the following cytokines is produced most abundantly by CD4+ T lymphocytes in allergic asthmatic airway inflammation?

A. Thymic stromal lymphopoietin  
B. Interferon gamma  
C. IL-12  
D. Granulocyte-macrophage colony-stimulating factor

9. A 37 year-old man with poorly-controlled asthma develops an acute asthma exacerbation in the setting of an upper respiratory infection. He has not been using his prescribed medications, which include a combined corticosteroid and long-acting beta-agonist inhaler and montelukast. Despite known sensitization to mouse, cockroach and dust mite, he has been unable to reduce exposure to these allergens in his home. When his wheezing and shortness of breath progress to the point where he can no longer walk across the room, he activates emergency medical services. He is found in extreme distress and is intubated in the field and brought to the nearest intensive care unit. Despite aggressive treatment measures, he passes away. Autopsy is performed and reveals, among other findings, significant mucus plugging of the airway lumina.

Which of the following pathologic findings contributes to increased mucus production in asthma?

A. Enlargement of alveolar mucus-secreting glands  
B. Increased airway mucosal vascularity  
C. Enlargement of mucus-secreting submucosal glands  
D. Epithelial goblet cell dysplasia

10. Which of the following viruses has been associated with asthma exacerbations?

A. Human rhinovirus species A  
B. Human rhinovirus species B  
C. Human rhinovirus species C  
D. Parainfluenza virus

Answers:

1. Answer B. Pages 990-991. Charcot-Leyden crystals. Charcot-Leyden crystals are crystals derived from lysed eosinophils. They may be found in mucus or mucus plugs and are one of several inflammatory changes that accompany severe asthma. See Figure 60-8D for a photograph of Charcot-Leyden crystals.

2. Answer C. Pages 990-991. Curschmann spirals. Curschmann spirals are distinctive spiral formations that may be found in mucus or sputum and are associated with inflammatory changes of severe asthma. See Figure 60-8C for a photograph of a Curschmann spiral.
3. Answer A. Page 994. Elevated exhaled fraction of nitric oxide. Airway epithelial cell nitric oxide production is increased in asthmatic inflammation. Measurement of the fraction of exhaled nitric oxide (FeNO) is considered a marker of eosinophilic asthma, and may predict response to steroid treatment in non-eosinophilic asthma. High levels of neutrophils or few or absent eosinophils in sputum may be associated with a poor response to corticosteroids. FEV1 may be reduced in either corticosteroid-responsive or corticosteroid-resistant asthma.

4. Answer B. Page 991. Inhibit neutrophil apoptosis. Corticosteroids selectively inhibit apoptosis of neutrophils, and promote apoptosis of eosinophils. Patients with asthma may develop neutrophilic inflammation in part as a result of corticosteroid treatment, though neutrophilic inflammation may also be promoted by Th17 type CD4+ T lymphocyte production of cytokines such as IL-17A.

5. Answer D. Pages 988-990. Increased alveolar tissue mast cell numbers. Remodeling in mild or moderate asthma, such as in the case of Mary, is characterized by thickening of the reticular basement membrane (also called the fibrillary layer or lamina reticularis), increased epithelial mucin-secreting goblet cells, enlarged bronchial submucosal mucus-secreting glands, thickening of the airway smooth muscle layer, and increased airway mucosal vascularity. Although in general the lung parenchyma is not primarily involved in asthma, alveolar mast cell numbers may be increased in uncontrolled asthma. This finding would be more likely to occur in Laura, whose asthma is poorly-controlled, than in Mary.

6. Answer C. Page 993. Within a few years of disease onset. Limited bronchial biopsy studies of asthma in childhood reveal that bronchial wall inflammation and evidence of remodeling may be found early in the course of disease. Findings include increased bronchial smooth muscle mass primarily due to myocyte hyperplasia. Reticular basement membrane thickening has been found in children with severe recurrent wheezing, though it has not been found in wheezy infants with reversible airflow obstruction.

7. Answer B. Page 992. CXCL5. CXCL5 is a chemoattractant present in the airway mucosa during asthma exacerbations. Its presence correlates with increased numbers of eosinophils. The other answers listed are chemokines that attract other types of cells of the immune system.

8. Answer D. Page 987. Granulocyte-macrophage colony-stimulating factor. In allergic asthma, CD4+ T lymphocytes play a key role in airway inflammation and evidence of remodeling may be found early in the course of disease. Findings include increased bronchial smooth muscle mass primarily due to myocyte hyperplasia. Thymic stromal lymphopoietin is related to Th2 differentiation of CD4+ T lymphocytes, but is not one of the key cytokines produced by Th2 type CD4+ T lymphocytes. Interferon gamma and IL-12 are Th1-type cytokines.

9. Answer C. Pages 989-990. Enlargement of mucus-secreting submucosal glands. Characteristic autopsy findings in patients who died of asthma include airway wall edema, inflammatory cell infiltration, epithelial shedding, and inspissated mucus plugging the airway lumina. Enlargement of mucus-secreting submucosal glands has been associated with fatal asthma, and is a feature of remodeling even in less severe asthma. Mucus-secreting glands are not found in the alveoli. Increased airway mucosal vascularity may contribute to airway wall edema, but is less likely to contribute to increased mucus production. Epithelial goblet cells undergo hyperplasia in large airways and metaplasia in small airways in asthma; goblet cell dysplasia is not a pathologic feature of asthma.
10. Answer C. Page 992. Human rhinovirus species C. Viral infections are a common trigger for asthma exacerbations, and may enhance the inflammatory response to allergen exposure. Rhinoviruses are the most common viruses to be implicated in asthma exacerbations, and human rhinovirus species C (HRV-C) is a subgroup of rhinovirus that is particularly associated with asthma exacerbations.
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**Review Questions**

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**Chapter 63 (pages 1032-1041): Approach to the Patient with Chronic Cough**

Prepared by: Rebecca Koransky, MD

1. Which of the following would you expect to be a cause of a subacute cough in adults?
   a. Smoking
   b. Common cold
   c. Allergic rhinitis
   d. Post-infectious cough

2. In children, to diagnose chronic cough, symptoms must be present for at least how long?
   a. 2 weeks
   b. 4 weeks
   c. 6 weeks
   d. 8 weeks

3. After ruling out smoking and ACE-inhibitor use in a patient with a chronic cough, what is the next step in management?
   a. Obtain CXR
   b. Obtain spirometry
   c. Obtain esophageal pH studies
   d. Empiric treatment with antihistamines, PPI, and bronchodilator

4. In adults, which of the following details in the history has been shown to be helpful in diagnosing the cause of a chronic cough?
   a. Character of cough
   b. Sound quality of cough
   c. Timing of cough
   d. Duration of cough

5. Which of the following provides the correct diagnosis of chronic bronchitis?
a. Exposure to respiratory irritant, productive cough on most days during three consecutive months for two consecutive years
b. Exposure to respiratory irritant, dry cough on most days over six consecutive months for two consecutive years
c. Exposure to cigarette smoke only, dry cough, on most days over two years
d. Exposure to cigarette smoke only, productive cough, on most days during three consecutive months for one year

6. Which of the following is responsible for the most cases of upper airway cough syndrome?
   a. Nonallergic rhinitis
   b. Allergic rhinitis
   c. Bacterial sinusitis
   d. Fungal sinusitis

7. What would be appropriate treatment of vasomotor rhinitis leading to upper airway cough syndrome?
   a. Budesonide nasal spray
   b. Ipratropium bromide nasal spray
   c. Montelukast
   d. Loratadine

8. Which of the following is characteristic of NAEB (nonasthmatic eosinophilic bronchitis) only and not asthma?
   a. Chronic cough can be the only presenting symptom
   b. Positive methacholine challenge test
   c. Mast cells present in airway mucosa but not in smooth muscle layer
   d. Sputum eosinophilia

9. In children, which two diseases are the most common causes of nonspecific chronic cough?
   a. UACS and Asthma
   b. GERD and Asthma
   c. Asthma and bacterial bronchitis
   d. UACS and bacterial bronchitis

10. Empiric treatment is often started in patients with chronic cough, with patients then monitored for improvement. Which etiology below is paired with the correct length of time before symptoms are expected to improve from treatment and the effect of treatment can be fully assessed?
    a. Asthma - 1 week
    b. UACS - 2 weeks
    c. GERD - 3 months
d. Smoking - 2 months

Answers:

1. **D. Page 1032, 1035.** Subacute cough has a duration of 3-8 weeks. Of the listed choices, only post-infectious cough is expected to fit that duration. The common cold is a cause of acute cough, and both smoking (via chronic bronchitis) and allergic rhinitis can lead to a chronic cough.

2. **B. Page 1032.** In children, cough is defined as acute (< 4 weeks) or chronic (> 4 week). Subacute cough is not defined in children.

3. **A. Page 1038.** The next step in management is to obtain a chest x-ray. If the x-ray is normal, then this patient represents the “clinical profile” of cough usually associated with UACS (upper airway cough syndrome), asthma, NAEB (nonasthmatic eosinophilic bronchitis), or GERD. Once a normal x-ray is obtained, empiric therapy can be started based on the history.

4. **D. Page 1033.** In evaluating a patient with a cough, it is important to first obtain a detailed history. The character of cough (productive, dry), sound quality (barking, honking), and timing (nocturnal) have not been proven to help in diagnosis. Determining the duration of cough, however, can help guide the differential. If the cough is determined to be chronic, UACS, asthma, NAEB, and GERD have been proven to be the most likely causes.

5. **A. Page 1035.** Chronic bronchitis can be diagnosed in patients with exposure to respiratory irritants (dust, fumes, smoke). Patients must expectorate phlegm on most days for three consecutive months over two consecutive years. Other common causes of cough-phlegm syndrome (e.g., UACS, bronchiectasis, asthma, GERD) must be ruled out and the cough must resolve after elimination of irritant.

6. **C. Page 1035.** Of the causes listed, bacterial sinusitis accounts for the most cases of chronic cough (39% of cases) due to UACS. The next most frequent is nonallergic rhinitis, followed by allergic rhinitis.

7. **B. Page 1037.** Vasomotor rhinitis is treated with ipratropium nasal spray. The other medications can be used to treat allergic rhinitis.

8. **C. Page 1037.** In NAEB mast cells are present in the airway mucosa only. In asthma, mast cells are present in the airway mucosa, submucosa, and smooth muscle layer. Methacholine challenge test would be negative in NAEB but positive in Asthma. Chronic cough as the only symptom, sputum eosinophilia, and a response to inhaled steroids can be seen in both asthma and NAEB.
9. **C. Page 1038-1039.** In children, chronic cough is divided into specific and nonspecific categories. A nonspecific cough is a cough that occurs on its own. In children, asthma and protracted bacterial bronchitis have been shown to be the most common causes of nonspecific cough.

10. **C. Page 1039.** It is important to ensure that patients complete a full course of treatment before determining that a treatment has failed. Asthma and UACS can take up to 4 weeks to improve, chronic bronchitis from smoking can take up to 4 weeks after stopping smoking, to improve and GERD can take up to 3 months to improve and 5-6 months to resolve.
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**Chapter 65 (pages 1056-1065): Lung Imaging**
Prepared by: Shabab Virani, MD

1. Which of the following statements about airway wall thickening in asthma is true?
   a. Airway wall thickening correlates with airflow limitation
   b. Airway wall thickening correlates with airway hyperresponsiveness
   c. Airway wall thickening correlates with air trapping on expiratory CT
   d. a, b, and c are all true

2. Which of the following pathologic changes does NOT occur in airway remodeling?
   a. Thickening of the reticular basement membrane
   b. Granuloma formation
   c. Thickening of airway smooth muscle
   d. Glandular hyperplasia

3. Which of the following statements are true?
   a. CT-assessed airway remodeling correlates with duration of asthma
   b. Functional imaging has been unable to document ventilation defects in asthma
   c. MRI with hyperpolarized helium-3 (HP He) is able to provide 3D images of lung ventilation at spatial resolutions from 3 to 5 mm
g   d. Ventilation defects in healthy subjects is relatively uncommon

4. What is the serious safety concern with use of MRI with hyperpolarized helium-3 (HP He)?
   a. MRI with HP He is generally considered safe
   b. Patients receive high doses of ionizing radiation
   c. Patients experience respiratory exacerbations
   d. Patients experience prolonged hemoglobin desaturation secondary to He-N₂ gas mixture

5. What is the mostly commonly used molecule in PET imaging?
   a. Fluoride-18
   b. Carbon-11
   c. Oxygen-15
   d. \(^{18}\text{F-fluorodeoxyglucose}\)
6. In a FDG-PET performed to evaluate lung inflammation in asthma, which cell type is the primary reason for causing an increased FDG signal that indicates lung inflammation?
   a. Basophils  
   b. Neutrophils  
   c. Eosinophils  
   d. Lymphocytes

7. How much more radiation on average is delivered with a CT chest compared to a posterior-anterior chest radiograph?
   a. 10-60 times more radiation is delivered with a CT chest
   b. 60-120 times more radiation is delivered with a CT chest
   c. 120-180 times more radiation is delivered with a CT chest
   d. 180-240 times more radiation is delivered with a CT chest

8. Which of the following was found NOT to be significantly correlated with air trapping in asthma?
   a. Severe refractory asthma as defined by ATS criteria
   b. Asthma-related hospitalizations
   c. Intensive care unit hospitalizations
   d. Need for mechanical ventilation

9. What is the role of imaging in diagnosis and treatment of asthma?
   a. Imaging helps to evaluate for other possible diseases
   b. Imaging can be useful in providing a reproducible and noninvasive biomarker that can help evaluate clinical interventions over time
   c. Imaging can be useful in evaluating underlying lung function and physiology
   d. All of the above

10. In asthmatic patient, which of the following statements about airway wall thickening seen on CT chest is true?
    a. Airway wall thickening is associated with increased intraepithelial neutrophils
    b. Airway wall thickening is associated with increased intraepithelial eosinophils
    c. Airway wall thickening is associated with increased exhaled nitric oxide
    d. CT airway measures do not appear to provide an adequate measure of airway inflammation
Answers:

1. D. page 1057. Airway wall thickening in asthma has been shown to correlate with airflow limitation, airway hyperresponsiveness, and air trapping on expiratory CT.
2. B. page 1056. Airway remodeling in asthma is characterized by thickening of the reticular basement membrane due to matrix deposition, thickening of airway smooth muscle, and glandular hyperplasia.
3. C. pages 1057, 1058, 1059. MRI with HP He is unique in that compared to other methods it is able to provide 3D images of ventilation with whole-lung coverage at spatial resolutions from 3 to 5 mm. CT-assessed airway remodeling does NOT correlate with duration of asthma. Functional imaging of lung ventilation using all three major platforms (CT, MR, and PET) has been able to document ventilation defects (large subsegmental and segmental defects) in asthma. Ventilation defects in health subjects is relatively common.
4. A. page 1058. MRI with HP He is generally considered safe. There is no ionizing radiation dose. Mild adverse events have been reports in fewer than 10% of patients undergoing the scan. The primary safety concern is the anoxic He-N2 gas mixture as it displaces air in the lungs. But even with breathholds of 10 to 20 seconds, the hemoglobin saturation rarely falls below 90% and it recovers to normal within seconds.
5. D. page 1061. The most commonly used molecule is 18F-fluorodeoxyglucose (FDG).
6. B. page 1062. Primed and activated neutrophils are the main source of an increased FDG signal.
7. B. page 1062. On average a CT chest delivers 60-120 times more radiation than a posterior-anterior chest radiograph.
8. A. page 1058. Air trapping in asthma as visualized on imaging was not significantly correlated with severe refractory asthma.
9. D. Imaging in asthma over the years has played an important role in better understanding the disease, monitoring disease activity, and evaluating other pulmonary diseases presenting similarly to asthma.
10. D. page 1057. CT airway measurements do not appear to provide an adequate measure of airway inflammation. There is currently weak to little evidence linking airway wall thickening to airway inflammation biomarkers.
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**Chapter 66 (pages 1066-1082): Aerosol and Aerosol Drug Delivery Systems**
Prepared by: Aba Al-Kaabi, MD

1. What term defines the mass of drug emitted per actuation that is actually available for inhalation at the mouth?
   a. Labeled dose (LD)
   b. Fine particle dose (FPD)
   c. Emitted dose (ED)
   d. Fine particle fraction (FPF)

2. Which of the following factors predict deposition and therapeutic effect of an aerosol?
   a. Fine particle fraction (FPF)
   b. Mass median aerodynamic diameter (MMAD)
   c. Fine particle dose (FPD)
   d. Geometric standard deviation (GSD)

3. Which of the following is the primary determinant of the site of lung deposition, distribution of the drug within the lung, and resulting deposition efficiency?
   a. Inspiratory flow rate
   b. The size of an aerosol particle
   c. Breath hold
   d. Sedimentation rate

4. As the mass of an aerosol particle decreases and the air stream velocity decreases, particles smaller than 5 µm tend to deposit on which of the following airways?
   a. Small airways
   b. Large airways
   c. Medium airways
   d. Very large airways

5. In addition to the particle size, what additional factor may make it possible to target specific regions in the lung for therapy?
   a. Inspiratory flow rate
   b. Expiratory flow rate
   c. Total lung deposition
   d. Inspiratory to expiratory ratio
6. Nebulizers are used for liquid formulations. Which of the following describes a jet nebulizer?
   a. A jet nebulizer incorporates a piezoelectric crystal, which is vibrated at a high frequency with sufficient intensity to create standing waves on the surface of the liquid overlying the crystal
   b. A jet nebulizer uses compressed air or oxygen to break up a thin film or jet of fluid into droplets suitable for inhalation
   c. A jet nebulizer generates aerosol only during inspiration, eliminating wastage of aerosol during exhalation and increasing the delivered dose threefold or higher
   d. A jet nebulizer has a design feature that vents supplemental air into the nebulizer across the venturi jet in the nebulizer bowl

7. Most current ultrasonic nebulizers producing aerosols operate at frequencies above what MHz?
   a. 1
   b. 10
   c. 100
   d. 1000

8. Which Albuterol Aerosol does not include alcohol?
   a. Proventil HFA
   b. ProAir HFA
   c. Xopenex HFA
   d. Ventolin HFA

9. Which HFA inhaled corticosteroids does not have a dose counter?
   a. Flovent HFA
   b. Aerospain HFA
   c. Qvar
   d. Alvesco HFA

10. Adding which of the following to the standard therapy for cystic fibrosis produces sustained improvement in lung function for up to 52 weeks?
    a. Dry powder Mannitol
    b. Olodaterol HCl
    c. Atenolol
    d. Metoprolol
Answers:

1. **C, page 1067.**
   The mass of drug emitted per actuation that is actually available for inhalation at the mouth is the emitted dose or delivered dose.

2. **A, page 1067.**
   Traditionally, the prediction of deposition efficiency for a therapeutic aerosol has been based on its mass median aerodynamic diameter (MMAD), which is determined by its particle size distribution. More recently, predictions of deposition and therapeutic effect of an aerosol have been based on its fine particle fraction (FPF)—the fraction of particles that can achieve deposition in the lower respiratory tract.

3. **B, page 1068.**
   The size of an aerosol particle is the primary determinant of the site of lung deposition, distribution of the drug within the lung, and resulting deposition efficiency.

4. **A, page 1068.**
   Particles smaller than 5 µm tend to deposit by sedimentation and diffusion on successively smaller airways as the mass of an aerosol particle decreases and the air stream velocity decreases.

5. **A, page 1069.**
   It may be possible to target specific regions in the lung for therapy by selection of particle size and inspiratory flow rate.

6. **B, pages 1072-1074.**
   Jet Nebulizers are nebulizers that use compressed air or oxygen to break up a thin film or jet of fluid into droplets suitable for inhalation.

7. **A, page 1073.**
   Most current ultrasonic nebulizers operate at frequencies above 1 MHz, producing aerosols with MMADs between 2 and 12 µm, with an output that is two to three times higher than with most jet nebulizers.

8. **D, page 1076.**
   The albuterol aerosol that does not include alcohol is Ventolin HFA.

9. **C, page 1076.**
   The HFA inhaled corticosteroids that does not have a dose counter is Qvar.

10. **A, page 1080.**
    A new study has shown that adding inhaled dry powder mannitol to standard therapy for cystic fibrosis produces sustained improvement in lung function for up to 52 weeks.
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**Chapter 73 (pages 1175-1185): Human Immunodeficiency Virus and Allergic Disease**

Prepared by: Catherine Crawford, MD

1. Mutations in the gene which encodes which chemokine receptor protects human cells from HIV infection?
   - a. CXCR1
   - b. CCR5
   - c. CXCR13
   - d. CCR8

2. A 3-month-old infant presents for evaluation of frequent infections. She has had thrush several times which is refractory to topical antifungal agents and suffers from chronic diarrhea and failure to thrive. Her mother was recently diagnosed with HIV (subtype B) infection and believes that she may have been infected while she was pregnant with her daughter. What is the test of choice for diagnosis of HIV in this infant?
   - a. HIV DNA PCR
   - b. ELISA for antibodies against HIV-1
   - c. HIV Western Blot
   - d. HIV-1/HIV-2 differentiation immunoassay

3. Which chemokine produced by CD8+ T cells can suppress viral replication of HIV by inhibiting viral entry into cells via CCR5?
   - a. IFN-γ
   - b. TNF-α
   - c. IL-4
   - d. RANTES

4. A component of many HAART regimens, which nucleoside reverse transcriptase inhibitor causes a potentially fatal hypersensitivity reaction in patients, more commonly in HLA B5701-positive individuals?
   - a. Zidovudine
   - b. Emtricitabine
   - c. Abacavir
   - d. Lamivudine
5. Compared to the general population, how many times higher is the risk of patients with AIDS of developing Stevens-Johnson syndrome, toxic epidermal necrosis, or other severe cutaneous drug reactions?
   a. 10
   b. 50
   c. 100
   d. 1000

6. A 46-year-old female presents with new-onset wheezing and shortness of breath with evidence of reversible obstruction on spirometry. Past medical history is pertinent for recent diagnosis of HIV and initiation of HAART and appropriate prophylaxis for low CD4+ T cell count noted in initial evaluation and work-up. This patient is diagnosed with asthma, likely related to the use of which medication(s)?
   a. Azithromycin
   b. HAART therapy
   c. TMP-SMX
   d. Dapsone

7. A 38-year-old man presents with weight gain, central obesity, striae, and easy bruising after initiating HAART therapy. Past medical history includes asthma for which he takes high-dose inhaled fluticasone twice daily. Which component of his HAART therapy may have led to this presentation?
   a. Ritonavir
   b. Atazanavir
   c. Indinavir
   d. Tipranavir

8. In HIV-infected patients with refractory atopic dermatitis, the use of oral antibiotics should be considered due to a documented high rate of skin colonization among these patients with which bacteria?
   a. Staphylococcus epidermidis
   b. Streptococcus pyogenes
   c. Pseudomonas aeruginosa
   d. Staphylococcus aureus

9. Which of the following cytokines binds CD25+ lymphocytes and regulates the proliferation and differentiation of both T and B lymphocytes, and is decreased in both acute and chronic HIV infection and is inversely correlated with viremia?
   a. IFN-γ
   b. IL-4
   c. IL-2
   d. IL-10
10. IL-4 production is increased in some stages of HIV-1 infection, leading to increased levels of IgE and upregulation of a chemokine receptor that causes increased entry of lymphocytotropic HIV-1 strains in CD4+ T cells. Which of following is that particular cytokine receptor?
   a. CXCR5  
   b. CXCR4  
   c. CXCL1  
   d. CCR2

**Answers:**

1. B. Page 1176. HIV requires CD4 and co-receptors to infect target cells. One of these co-receptors is the chemokine receptor CCR5. CCR5 and CXCR4 are the chemokine co-receptors used by most HIV viruses with CCR5 being the co-receptor for macrophage-tropic HIV strains. Mutations in the gene for this chemokine receptor make it more difficult for HIV strains to bind and enter the human cell, and then incorporate HIV RNA into the host genome.

2. A. Page 1176-7. In patients younger than 18 months of age, nonserologic tests must be used to establish the presence of HIV infection. Antibody-based tests can give false positives due to the potential for lingering maternally-derived anti-HIV antibodies. False negatives can also occur in young patients or in patients with impaired humoral immune responses as they may not produce antibody to the virus. HIV Western blot and the HIV-1/2 differentiation immunoassay are confirmatory tests to be used in the circumstance of a positive ELISA screening test. These tests are not typically used alone and are still dependent on antibody production. PCR can be less sensitive in non-subtype B infections.

3. D. Page 1178. CD8+ T cells produce a number of cytokines and chemokines which help to suppress HIV infection. RANTES, IL-10, and MIP-1β suppress viral replication by inhibiting viral entry into the cells via CCR5. IFN-γ induces the production of cellular proteins which suppress viral replication once HIV has entered the cell, and TNF-α promotes apoptosis of HIV-infected cells. IL-4 can be increased in HIV-1 infection patients but does not play a role in viral suppression.

4. C. Page 1180. Abacavir (ABC) causes a potentially fatal systemic illness in up to 8% of patients, typically within the first 9-11 days of treatment. Manifestations of this illness include high fever, diffuse rash, malaise, nausea, myalgia, arthralgia, and abdominal pain. Treatment-naïve white patients with higher CD8+ T cell counts at treatment initiation are at higher risk, and the HLA B5701 allele is the dominant risk factor for this hypersensitivity with a PPV greater than 70%. Lack of this allele has a NPV of 95-98%. Prescreening for this allele before starting ABC is now recommended. If signs of hypersensitivity occur, this drug must be discontinued and can never be safely reintroduced.

5. D. Page 1179. Drug hypersensitivity, including to common treatment agents such as Bactrim and mainstays of HAART, is relatively common in HIV-infected patients. Although the mortality rate is similar to that of the general population with these reactions, patients with AIDS have up to a 1000 times greater chance of developing SJS, TEN, or another severe cutaneous drug reaction.
6. B. Page 1182. Several studies have shown increased incidence of asthma in patients on HAART, thought to be due to immune reconstitution after initiation of this therapy. In some of these studies, CD4+ T cell reconstitution is correlated with asthma occurring in a greater proportion in patients with CD4+ T cell counts above 200/µL.

7. A. Page 1185. An important fact to remember when treating asthma in HIV-infected patients is the interaction between fluticasone and ritonavir, the concurrent use of which has been shown to lead to increased serum levels of fluticasone and potential side effects associated with exogenous corticosteroid use, including Cushing syndrome and adrenal suppression.

8. D. Page 1184-5. The association between HIV and increased rates of atopic dermatitis is unclear with studies previously reporting increased, decreased, and similar rates in incidence among HIV-infected and non-HIV-infected patients. Many other pruritic skin conditions occur in HIV-infected patients and can mimic this disease. Thirty to fifty percent of HIV-seropositive patients are colonized with S. aureus with many of these strains secreting superantigens, and in refractory cases of atopic dermatitis, treatment with oral antibiotics should be considered over corticosteroids which can lead to further immunosuppression of these patients.

9. C. Page 1178-9. Interleukin-2, a cytokine secreted by T lymphocytes, is decreased in both acute and chronic HIV infection. Infusions of IL-2 have previously been shown to lead to significant increases in CD4+ T cell count in patients with CD4+ T cell counts greater than 200/µL. This cytokine is also an important growth factor for regulatory T cells. IFN-γ and IL-10 are increased in HIV infection, and IL-4 can be increased or remain stable compared to non-HIV-infected individuals.

10. B. Page 1176-1179. IL-4 is increased in some stages of HIV-1 infection, leading to increased levels of IgE and contributing to the alteration of the Th1/Th2 balance in HIV-infected patients. Increased levels of IL-4 and IgE have been noted in more symptomatic patients. CXCR4 is the co-receptor for the fusion of lymphocytotrophic HIV strains while CCR5 is the co-receptor for macrophage-trophic strains, and CXCR4 is upregulated by IL-4. These two chemokine co-receptors are the most commonly used receptors by HIV strains to enter lymphocytes.
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Chapter 77a (pages 1237-1246): Anaphylaxis
Prepared by: Jackie Eastman, MD

1. Which of the following is not part of the criteria for anaphylaxis?
   a. Acute onset (minutes to hours)
   b. Involvement of the skin and/or mucosal tissues including hives, flushing or swelling
   c. Persistent GI symptoms including crampy abdominal pain and vomiting
   d. Hypertension

2. Females over age 15 have higher rate of anaphylaxis than males. The reason for this is unknown but may be due to which of the following?
   a. Increased incidence of food allergies
   b. Increased exposure to stinging insects
   c. Hormonal changes, such as progesterone, which increases sensitivity to anaphylaxis in animal models
   d. Reporting bias since females more likely to seek medical care for anaphylaxis

3. The main categories of anaphylaxis include which of the following?
   a. Anaphylactoid, allergic anaphylaxis, idiopathic
   b. Immunologic, idiopathic, food-induced, drug-induced
   c. Immunologic (IgE dependent and independent), nonimmunologic, idiopathic
   d. Immunologic (IgE dependent and independent), anaphylactoid, idiopathic

4. Which of the following is not a mediator of anaphylaxis?
   a. Histamine
   b. CRP
   c. Platelet-activating factor
   d. Leukotrienes

5. Platelet-activating factor has been shown to be important for anaphylaxis due to its role in which of the following?
   a. Smooth muscle contraction
   b. Clotting and disseminated intravascular coagulation
   c. Vascular permeability
   d. Inotropy
6. IL-33 may be important in anaphylaxis due to its role in which of the following?
   a. Direct induction of degranulation and cytokine production in IgE-sensitized mast cells
   b. Potentiation of IgE-mediated release of mediators from mast cells
   c. Activation of ILC2s leading to more cytokine release
   d. Chemotactic effect on eosinophils which contributes to late phase responses

7. Vasodilation in anaphylaxis is mediated by which of the following?
   a. H1 and H3 receptors
   b. H1 and H2 receptors
   c. H1 and H4 receptors
   d. H2 and H3 receptors

8. The main pathophysiologic feature of anaphylactic shock is which of the following?
   a. Fluid extravasation causing hemoconcentration and hypovolemia
   b. Profound bradycardia
   c. Increased intrathoracic pressure due to air trapping from bronchospasm
   d. Arterial vasodilation

9. Which of the following is not a compensatory mediator that is released to counteract anaphylactic shock?
   a. Epinephrine
   b. Angiotensin I
   c. IL-6
   d. Endothelin-1

10. The reason that initial treatment for anaphylactic shock is unsuccessful is most often due to which of the following?
    a. Insufficient fluid resuscitation
    b. Inadequate doses of epinephrine
    c. Need for atropine to treat bradycardia
    d. Insufficient use of antihistamines
Answers:

1. D. Page 1238. Hypertension is not part of the criteria for anaphylaxis.

2. C. Page 1239. Men are more likely to have anaphylaxis to stinging insects. Women report more anaphylaxis to medications. Adult females do report more food allergies than men, but this does not account for the increase in anaphylaxis.

3. C. Page 1241. The general categories are immunologic, idiopathic and nonimmunologic. Immunologic is split between IgE dependent (food, venom, drug) or IgE independent (aspirin, radiocontrast). Nonimmunologic includes exercise and physical factors.

4. B. Pages 1242 and 1244. CRP has been shown to increase as a marker of late phase reactions, but is not a known part of the pathogenesis of anaphylaxis.

5. B. Page 1243. PAF induces clotting and DIC. Levels of PAF have been shown to correlate directly with severity of anaphylaxis in humans.

6. A. Page 1243. In a mouse model, IL-33 was important for direct induction of cytokine and eicosanoid release from mast cells. Its role in humans is unclear, although levels have been shown to be higher in patients after perioperative anaphylaxis. IL-33 can stimulate ILC2s but it is unknown if this has any role in anaphylaxis.

7. B. Page 1243. H2 receptors directly act on smooth muscle cells and H1 receptors mainly work by stimulating endothelial cells to manufacture nitric oxide.

8. A. Page 1245. Fluid extravasation of up to 35% of circulating blood volume has been demonstrated. There is a relative bradycardia to level of hypotension, but this is not the main driver of shock. Arterial vasodilation has been postulated as a cause, but not proven. Air trapping does not have a role in causing anaphylactic shock.

9. C. Page 1246. IL-6 may be correlated with the degree of anaphylaxis but is not considered a compensatory mechanism. The others are released to compensate for hypotension.

10. A. Page 1246. Up to 5 L of fluid may be needed in the first 20 minutes to compensate for the extravasation of fluid. Epinephrine may not be adequately absorbed from hypoperfused muscle, but ultimately epinephrine alone cannot reverse anaphylactic shock. Atropine and antihistamines are also ineffective without adequate fluid resuscitation.
Welcome to the FIT Board Review Corner, prepared by Amar Dixit, MD, and Christin Deal, MD, senior and junior representatives of ACAAI's Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Middleton's Allergy Principles and Practice, 8th Edition
N. Franklin Adkinson Jr., MD, Bruce S Bochner, MD, A Wesley Burks, MD, William W Busse, MD, Stephen T Holgate, MD, DSc, FMedSci, Robert F Lemanske, Jr., MD and Robyn E O’Hehir, FRACP, PhD, FRCPATH

Chapter 77b (pages 1246-1255): Anaphylaxis
Prepared by: Tammy Peng, MD

1. Patients taking which of the following medications may have enhanced susceptibility to episodes of scombroidosis?
   a. Cephalosporins
   b. Griseofulvin
   c. Isoniazid
   d. Disulfiram

2. Elevated levels of which of the following hormones associated with menses may predispose patients to anaphylactoid reactions to the infusion of luteinizing hormone-releasing hormone (LHRH) and intradermal injections of medroxyprogesterone?
   a. Estrogen
   b. Progesterone
   c. Luteinizing hormone (LH)
   d. Follicle-stimulating hormone

3. Which of the following laboratory tests reaches peak levels at 60-90 minutes after onset of anaphylaxis?
   a. Serum catecholamines
   b. Plasma histamine
   c. Urinary histamine metabolites
   d. Serum tryptase

4. Which of the following medications interfere with endogenous compensatory responses to hypotension during anaphylaxis?
   a. ACE-inhibitors
   b. β-blockers
   c. Monamine oxidase inhibitors (MAOIs)
   d. Tricyclic antidepressants (TCAs)
5. Which of the following is the appropriate range of dosing and concentration of epinephrine to be administered to an adult intramuscularly in the lateral thigh?
   a. 0.1-0.3 mL of 1:10,000 solution
   b. 0.3-0.5 mL of 1:10,000 solution
   c. 0.1-0.3 mL of 1:1,000 solution
   d. 0.3-0.5 mL of 1:1,000 solution

6. What is the drug of choice in treatment of anaphylaxis in patients on β-blockers?
   a. Atropine
   b. Dopamine
   c. Glucagon
   d. Vasopressin

7. Which of the following is the best predictor for a serious recurrence of anaphylaxis?
   a. Asthma
   b. Ability to avoid exposures to triggering agents
   c. Serious symptoms at time of initial event
   d. Amount of allergen necessary to produce reaction

8. Based on a compilation of 1784 patients which were reviewed in a published series entitled “Anaphylaxis and anaphylactoid reactions,” the most common clinical manifestation of anaphylaxis is which of the following?
   a. Cutaneous symptoms
   b. Respiratory symptoms
   c. Gastrointestinal symptoms
   d. Cardiovascular symptoms

9. Which of the following describes non-IgE-mediated events compared to IgE-mediated events that occur in the operating room?
   a. Slightly lower incidence of cutaneous manifestations in operative non-IgE mediated events compared to operative IgE-mediated events
   b. Cardiovascular collapse occurs more often in operative non-IgE-mediated events than IgE-mediated events
   c. Surgical non-IgE-mediated events are more severe than surgical IgE-mediated events
   d. Wheezing and bronchospasm occurs more frequently in operative non-IgE-mediated events than operative IgE-mediated events
10. Which of the following predisposes one to a late phase response in anaphylaxis?
   a. Immediacy of symptoms
   b. Severity of the first response
   c. Delayed administration and underdosing of epinephrine
   d. Lack of corticosteroid administration
Answers:

1. C. Isoniazid, p. 1249 “Restaurant Syndromes and Scombroidosis”

Scombroidosis, which is histamine poisoning caused by ingestion of histamine in spoiled fish may mimic anaphylaxis. Patients taking isoniazid appear to have increased susceptibility to episode of scombroidosis. Alcohol-induced flush may also mimic anaphylaxis and has been linked to drugs including disulfiram, griseofulvin and cephalosporins.

2. B. Progesterone, p. 1250 “Other Differential Diagnoses”

Patients with progesterone-related anaphylactic episodes have anaphylactoid reactions with the infusion of LHRH and intradermal administration of medroxyprogesterone. The mechanism of this disorder is unknown but increased levels of progesterone associated with menses may predispose patients to anaphylactic events. LHRH analog therapy is beneficial. The disorder should be suggested in women, typically over age 35 with recurrent episodes of anaphylaxis with temporal relationship with menstrual cycle.

3. D. Serum Tryptase, p. 1250 “Laboratory Findings”

Serum tryptase levels peak 60-90 minutes after onset of anaphylaxis and persist longer than plasma histamine levels do. Elevated tryptase levels are sometimes seen up to 5 hours after symptom onset and rarely can persist several hours longer. Plasma histamine levels rise within 5-10 minutes of onset of anaphylaxis and remain elevated for 30-60 minutes. Urinary histamine metabolites are elevated for a longer period.

4. A. ACE-inhibitors, p. 1251 “Prevention and Management”

Patients who are at risk for anaphylaxis should not take the following medications if other agents will suffice: β-adrenergic blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), MAOIs and TCAs. ACE inhibitors and ARBs interfere with endogenous compensatory responses to hypotension. β-blockers decrease efficacy of epinephrine whereas MAOIs and some TCAs affect the use of epinephrine through side effects.

5. D. 0.3-0.5 mL of 1:1,000 solution, p. 1252 “Administered by Physician” and Table 77-7 “Drugs and Other Agents Used in Anaphylaxis Therapy”

The concentration of epinephrine for IM administration is 1:1000. The dose for adults is 0.3 to 0.5 mL of 1:1000 solution or 0.3 to 0.5 mg. In children, the dose of IM epinephrine is 0.01 mg/kg up to the maximal adult dose. The dose of epinephrine may be repeated two to three times as needed, at intervals of 5 to 15 minutes.

6. C. Glucagon, p. 1253-1254, Table 77-7 “Drugs and Other Agents Used in Anaphylaxis Therapy” and “Glucagon”

Patients taking β-blockers may demonstrate resistance to standard therapies for anaphylaxis
(epinephrine). Glucagon is the drug of choice in patients using β-blockers. Atropine is used for bradycardia. Dopamine is a vasopressor and the rate of infusion is titrated to blood pressure response. Vasopressin is an example of another vasoconstrictor besides epinephrine that may be used in cardiovascular collapse from anaphylaxis.

7. C. Serious symptoms at time of initial event, p. 1255 “Prognosis for Recurrence”

Prognosis for patients with recurrent anaphylactic episodes is reasonably good. Prognosis is based on natural history, amount of allergen necessary to produce reaction, and ability to avoid triggering agents. However, the best predictor for recurrence was presence of serious symptoms during initial event. In one study cited, neither asthma nor atopy were risk factors for recurrence of anaphylaxis.

8. A. Cutaneous symptoms p. 1246, “Signs and Symptoms” and Table 77-6 “Signs and Symptoms of Anaphylaxis: Frequency of Occurrence”

The reviewed series included one series of patients with exercise-induced anaphylaxis or idiopathic anaphylaxis, one series limited to pediatric patients and another limited to randomly selected patients of all ages. The most common manifestation in the cases were cutaneous, followed by respiratory, cardiovascular and gastrointestinal.

9. A. Slightly higher incidence of cutaneous manifestations compared to operative IgE-mediated events, p. 1247 “Signs and Symptoms”

Significant differences may exist between surgical IgE-mediated and non-IgE-mediated events. The incidence for cutaneous manifestations for operative IgE-mediated events is 75% and is slightly higher for non-IgE-mediated events. Cardiovascular collapse, wheezing and bronchospasm are significantly more common during IgE-mediated episodes in the operating room. Surgical IgE-mediated events are also more severe than non-IgE-mediated episodes.

10. C. Delayed administration and underdosing of epinephrine, p. 1247 “Signs and Symptoms”

Biphasic anaphylaxis describes an anaphylactic episode that can abate and then recur several hours after symptoms have disappeared. Most biphasic reactions occur within the first 8 hours after the first reaction has resolved, but recurrent episodes have been reported as late as 72 hours. Exact incidence of biphasic reactions is unknown but range from 1 to 20% in reports. The severity of the second response also ranges from mild to severe. Delayed administration and underdosing of epinephrine predisposes to late phase response. No clear evidence shows that recurrent response can be surprised by corticosteroids.
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**Review Questions**

**Allergy and Immunology Review Corner:** Middleton’s Allergy Principles and Practice, 8th Edition

N. Franklin Adkinson Jr., MD, Bruce S Bochner, MD, A Wesley Burks, MD, William W Busse, MD, Stephen T Holgate, MD, DSc, FMedSci, Robert F Lemanske, Jr., MD and Robyn E O’Hehir, FRACP, PhD, FRCPath

**Chapter 78 (pages 1260-1259): Insect Allergy**

Prepared by: Amar Dixit, MD

1. Which of the following options has listed the insect with its correct respective family?
   a. Bumblebee: Formicidae
   b. White-faced Hornet: Apidae
   c. Honeybee: Vespidae
   d. Fire Ant: Formicidae

2. Which one of the following families contains cross reactivity amongst the different genera?
   a. Apidae
   b. Vespidae
   c. Formicidae
   d. Hominidae

3. How effective is venom immunotherapy in preventing sting anaphylaxis?
   a. 25%-45%
   b. 45%-65%
   c. 65%-75%
   d. 75%-98%

4. In a patient who is negative to initial skin testing, how long after should skin testing be repeated?
   a. 2-4 weeks
   b. 4-6 weeks
   c. 6-8 weeks
   d. Never

5. Which of the following statement is correct?
   a. The major allergenic component of honeybee venom is phospholipase A.
   b. The major allergenic component of vespid venoms is antigen 4.
   c. Whole-Body Vespin extracts are as effective as Vespin venoms for immunotherapy.
   d. The degree of skin test sensitivity correlates reliably with the degree of sting reaction.
6. Which of the following statements is incorrect?
   a. The risk of recurrence in patients with a history of systemic reactions to stings is higher for those who are allergic to honeybee stings than those with vespid allergies.
   b. In a patient who has had previous systemic reactions the outcome of the next sting is unpredictable.
   c. It is uncommon for patients to have more severe reactions with each subsequent sting.
   d. Large local reactions are usually a precursor of systemic reactions.

7. Which of the following is the most reliable predictor of the severity of subsequent sting reactions?
   a. Severity of previous reaction
   b. Skin testing results
   c. Specific IgE results
   d. Platelet-activating factor level

8. Which of the following are the possible exceptions to extending venom immunotherapy beyond five years?
   a. Those treated for honeybee allergy.
   b. Those who had systemic reactions to an injection or sting while receiving venom immunotherapy.
   c. Those with elevated baseline serum tryptase levels.
   d. Those who had very severe sting reactions before treatment.
   e. All of the above

9. Which of the following insects most commonly cause systemic reactions from bites?
   a. Mosquito (Culicoidae)
   b. Horsefly (Tabanidae)
   c. Deerfly (Tabanidae)
   d. Kissing Bug (Triatoma)

10. What are the indications for starting venom immunotherapy?
    a. Patients with a positive venom skin test AND an elevated IgE level
    b. Patients with a history of previous systemic reactions to a sting
    c. Patients with a history of previous systemic reactions to a sting AND a positive venom skin test AND an elevated IgE level
    d. Patients with a history of previous systemic reactions to a sting AND EITHER a positive venom skin test OR an elevated IgE level
Answers:

1. D. page 1261. The honeybee, bumblebee, and sweatbee belong to the apidae family. The yellow jacket, yellow hornet, white-faced hornet, and paper wasp belong to the vespidae family. The fire ant, jack jumper ant, and harvester ant belong to the formicidae family.

2. B. page 1263. There is little to no cross reactivity amongst families. The vespid family has extensive cross-allergenicity of the venoms of different genera. It should be noted that within each genus there are some species even within the vespid family that have only limited cross-reactivity. The hominidae family is the family to which humans belong.

3. D. page 1260. Venom immunotherapy is 75-98% effective in preventing sting anaphylaxis. Of note, it is a safe as inhalant allergen immunotherapy.

4. B. page 1264. Some patients will have negative skin testing after a sting. This is attributed to a refractory period of anergy. The skin tests should be repeated after 4 to 6 weeks. It should be noted that some cases of sting anaphylaxis with negative skin testing may be because the sting anaphylaxis is due to non-IgE mediated process or a subclinical mastocytosis.

5. A. pages 1263 and 1265. The major allergenic component of honeybee venom is phospholipase A. The major allergenic component of vespid venoms is antigen 5. Whole-Body extracts (with the exception of fire ants) are NOT effective for immunotherapy. The degree of skin test sensitivity does NOT correlate reliably with the degree of sting reaction.

6. D. page 1266. Large local reactions are NOT usually a precursor of systemic reactions. Most individuals with local reactions consistently have similar reactions with repeated stings, even some whose family members have had systemic reaction. The risk of eventual anaphylaxis in those with large local reactions is only 5% to 10%.

7. A. page 1267. The severity of the previous sting reactions is the most reliable predictor.

8. E. page 1270. Generally, the published studies indicate venom immunotherapy can be stopped after 5 years with possible exceptions provided in answers a-d.

9. D. page 1270 and 1271. The most common cause of systemic reactions from insect bites is from the kissing bug.

10. D. page 1267. The indication for venom immunotherapy is patients with a history of previous system reactions to a sting AND evidence of venom-specific IgE antibodies (either a positive venom skin test result OR elevated specific IgE level).