



## **Allergy and Immunology Board Review Corner: 2020**

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## Review Questions

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N. Franklin Adkinson, Jr., Bruce S. Bochner, A. Wesley Burks, William W. Busse, Stephen T. Holgate, Robert F. Lemanske, Jr., Robyn E. O'Hehir

**Chapter 14:** Biology of Mast Cells and Their Mediators

Prepared by: Miriam Samstein MD PhD

1. IgE binds to which subunit of Fc $\epsilon$ RI?
  - a. Alpha
  - b. Beta
  - c. Gamma
2. What is the best marker of systemic mast cell activation in anaphylaxis?
  - a. Plasma histamine
  - b.  $\alpha$ -tryptase
  - c. B-tryptase
  - d. chymase
3. The Early Asthmatic Reaction is a decline in respiratory function within how many minutes of bronchial allergen challenge?
  - a. 10-20 minutes
  - b. 60-90 minutes
  - c. 90-180 minutes
  - d. 4 hours
4. Which of the following is an obligate mast cell growth factor?
  - a. VEGF
  - b. SCF
  - c. GCSF
  - d. GMCSF
5. The arachidonic acid metabolite prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is synthesized by which pathway?
  - a. Lipoxygenase pathway
  - b. Pyruvate pathway
  - c. IRAK
  - d. cyclooxygenase

6. The generation of IP<sub>3</sub> following IgE dependent mast cell stimulation leads to:
  - a. Efflux of intracellular CA<sup>2+</sup> and storage of Ca<sup>2+</sup> in the rough endoplasmic reticulum
  - b. Ca<sup>2+</sup> mobilization from the rough endoplasmic reticulum and influx of extracellular Ca<sup>2+</sup>
  - c. Activation of the NOD2 pathway
  - d. Activation of the sodium calcium transporter on the rough endoplasmic reticulum
7. Mast cells are thought to skew T cell development towards which phenotype?
  - a. Th1
  - b. Th2
  - c. Th17
  - d. Treg
8. Anaphylaxis is primarily mediated by which two cell types?
  - a. Mast cells and eosinophils
  - b. Eosinophils and basophils
  - c. Neutrophils and eosinophils
  - d. Mast cells and basophils
9. The percentage of which type of mast cell is increased in the skin of patients with atopic dermatitis?
  - a. MC<sub>TC</sub>
  - b. MC<sub>TCT</sub>
  - c. MC<sub>T</sub>
  - d. MC<sub>c</sub>
10. Aspirin-triggered asthma is associated with?
  - a. Increased LTE<sub>4</sub> in the urine
  - b. Increased LTE<sub>4</sub> in nasal secretions
  - c. Increased PGD<sub>2</sub> in the urine
  - d. Decreased PGD<sub>2</sub> in the urine

**Answers:**

1. **A.** Page 233. FcεRI is a tetrameric structure consisting of an alpha chain that binds IgE, a beta chain signaling subunit and two gamma subunits that exist as immunoreceptor tyrosine-based activation Motif (ITAM) – containing homodimer signaling subunit.
2. **C.** Page 237. The best marker of systemic mast cell activation in anaphylaxis is an acute rise in the concentration of B-tryptase in the peripheral circulation. Alpha tryptase is released by mast cells constitutively, B tryptase is stored in mast cell granules and released after IgE-dependent activation. Histamine concentrations in blood peak within 5 minutes, the tryptase concentration is maximal between 15 and 120 minutes after the onset of symptoms.
3. **A.** Page 239. The early asthmatic response is a rapid deterioration of pulmonary function, as indicated by a fall in forced expiratory volume in 1 second, at 10 to 20 minutes following bronchial allergen challenge.

4. **B.** Page 228. Stem cell factor (SCF), or kit ligand, is an obligate mast cell growth factor that is derived from many cellular sources. Removal of SCF leads to rapid mast cell apoptosis. SCF is the ligand for kit encoded by the proto-oncogene c-kit.
5. **D.** Page 233. Newly formed metabolites of arachidonic acid are released from mast cells after IgE-dependent activation. The cyclooxygenase pathway produces PGD<sub>2</sub>, whereas the lipoxygenase pathway form Leukotriene C<sub>4</sub> (LTC<sub>4</sub>).
6. **C.** Page 234. IgE receptor activation initiates receptor aggregation with lipid rafts containing Lyn. Lyn kinase transphosphorylates tyrosine residues on the ITAMS binding to phosphorylated FC $\epsilon$ R $\beta$ 1 ITAM through the src homology 2 domain. Syk protein tyrosine kinases are recruited to the rafts and bind the phosphorylated ITAMS. They are then phosphorylated to recruit Lyn and Syk promoting an activation loop. This results in fully activated Syk, starting a cascade that activates inositol triphosphate (IP<sub>s</sub>). IP<sub>3</sub> induced CA<sup>2+</sup> mobilization from the rough endoplasmic reticulum stores which initiates influx of extracellular Ca<sup>2+</sup>, a critical requirement for the release of preformed and newly generated mediators.
7. **B.** Page 237. Rat mast cells can skew T cell differentiation towards a Th2 phenotype through IL-4 release. Mast cells also influence the development of dendritic cells and their ability to activate T cells. Histamine increases IL-10 and decreases IL-12 production by mature dendritic cells, polarizing naïve T cells towards a Th2 phenotype.
8. **D.** p. 237. Anaphylaxis is mediated primarily by mast cells and perhaps basophils.
9. **C.** p. 239. Healthy skin contains mast cells that are approximately 90% MC<sub>Tc</sub>. The number of MC<sub>T</sub> increases in the skin of patients with atopic dermatitis.
10. **A.** p. 241. Aspiring-triggered asthma is associated with increased LTC<sub>4</sub> in the nasal secretions and increased LTE<sub>4</sub> in the urine.



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### Chapter 15: Biology of Basophils

Prepared by: Diana Rangel, MD

1. Where do the basophils develop?
  - a. Liver
  - b. Thymus
  - c. Fetal Liver
  - d. Bone marrow
  
2. Which precursor cells differentiate into cells that morphologically and functionally resemble basophils?
  - a. CD4+
  - b. CD8+
  - c. CD19+
  - d. CD34+
  
3. Which of the following cytokines play a significant role in the survival and activation of mature basophils?
  - a. IL-3
  - b. IL-4
  - c. IL-5
  - d. IL-13
  
4. If there is an exposure to an allergen, the bone marrow activates and increases the production of the following cells:
  - a. Basophils and eosinophils
  - b. Basophils and mast cells
  - c. B cells and eosinophils
  - d. B cells and mast cells

5. Basophils have the ability to infiltrate into tissue sites. These “rolling” events are mediated through the expression of which of the following?
  - a. L-selectin (CD62L)
  - b.  $\beta$ 1- and  $\beta$ 2-integrin
  - c.  $\beta$ 1-integrin very late antigen (VLA)-4
  - d. Intracellular adhesion molecules (ICAMs)
  
6. Which of the following cytokines inhibits the priming effects that IL-3 has on basophil function?
  - a. TNF
  - b. IFN- $\gamma$
  - c. IFN- $\beta$
  - d. GM-CSF
  
7. How do basophils provide signals for B cells to produce IgE?
  - a. Expressing CD63 and secreting IL-4 and IL-13
  - b. Expressing CD32 and secreting IL-4 and IL-13
  - c. Expressing CD40L and secreting IL-4 and IL-13
  - d. Expressing CD203c and secreting IL-4 and IL-13
  
8. Which of the following markers has been used as a means for determining basophil activation?
  - a. CD63 and CD203c
  - b. CD117 and CD32
  - c. CD40L and CD23
  - d. CD11c/CD18
  
9. Which of the following basophil receptors is associated with innate immunity?
  - a. CCR3
  - b. IL-1 like receptor
  - c. Toll-like receptors
  - d. Receptors for prostacyclin
  
10. Mast cells and basophils differ with respect to the mediators they release. Which of the following is not secreted by basophils on Fc $\epsilon$ RI-mediated activation?
  - a. Histamine
  - b. PGD<sub>2</sub>
  - c. LTC<sub>4</sub>
  - d. IL-3

**Answers:**

- 1. D.** Page 252. Like all granulocytes, basophils are of myeloid origin, developing from pluripotent stem cell precursors found in the bone marrow.
- 2. D.** Page 252. CD34+ precursor cells, when cultured in the presence of IL-3, differentiate into cells that morphologically and functionally resemble basophils.
- 3. A.** Page 252. IL-3 plays a significant role in the survival and activation of mature basophils. This is a functional consequence of these cells' retaining the expression of IL-3 receptors (CD123) at remarkably high levels.
- 4. A.** Page 253. The frequencies of these precursor cells are increased in asthmatics and in subjects who have undergone experimental allergen provocation, suggesting a positive feedback mechanism by which exposure to allergen results in bone marrow activation and increased production of both basophils and eosinophils.
- 5. A.** Page 253. As with other leukocytes, the initial steps of basophil attachment to endothelium occurs during "rolling" events, in which selectins play a critical role. This is mediated through the expression of L-selectin (CD62L), which attaches to the ligands CD34 and MAcAM-1.
- 6. C.** Page 254. Basophils express the major receptor (IFN $\alpha$ R1) that binds these cytokines, and both IFN- $\alpha$  and IFN- $\beta$  inhibit the priming effects that IL-3 has on basophil function.
- 7. C.** Page 254. By expressing CD40L and secreting IL-4 and IL-13, basophils have the potential to provide the two necessary signals for B cells to produce IgE.
- 8. A.** Page 254. In recent years, the increased surface expression of CD63 and CD203c has been widely used as a means for determining basophil activation.
- 9. C.** Page 255. Basophils have recently been found to express two additional types of innate immunity-associated receptors: (1) Toll-like receptors (e.g., TLR1, -2, -4, -6, -9), which bind a variety of microbial products, and (2) leukocyte immunoglobulin-like receptors (e.g., LIR3, -7), for which the natural ligands have not yet been identified.
- 10. B.** Page 260. Ultimately, in vitro studies showed that mast cells and basophils differ with respect to the mediators they release and the way in which they respond to various stimuli. For example, mast cells secrete PGD<sub>2</sub> on Fc $\epsilon$ RI-mediated activation, whereas basophils do not.



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### Chapter 16: Biology of Eosinophils

Prepared by: Stephani Lynn Mawhirt, DO

1. Which of the following substances are contained within eosinophilic "specific" or secondary granules?
  - a. Charcot-Leyden crystal protein
  - b. major basic protein
  - c. CD11b
  - d. acid phosphatase
2. Eosinophil production and lineage differentiation is dependent on which transcription factor?
  - a. GATA-1
  - b. GATA-3
  - c. GATA-6
  - d. GATA-8
3. Eosinophil proliferation and differentiation is dependent upon interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-5 (IL-5). Committed eosinophil precursors in the bone marrow can be identified by their expression of which of the following?
  - a. IL-3 receptor and CCR5
  - b. IL-5 receptor and CCR3
  - c. IL-3 receptor and CCR7
  - d. IL-5 receptor and CXCL13
4. Eosinophils are primarily located in tissues including the thymus, uterus, mammary glands, and gastrointestinal tract (except the esophagus) where their life span is about 2-5 days. In the peripheral blood, eosinophil half-life is about 8-18 hours. Measurement of eosinophils in the blood are the highest at what time of day?
  - a. early morning
  - b. late morning
  - c. mid afternoon
  - d. evening

5. A correlation between the concentration of this specific granule protein measured in bronchoalveolar lavage fluid with the severity of bronchial hyper-reactivity has been observed in patients with asthma:
  - a. major basic protein
  - b. eosinophil cationic protein
  - c. eosinophil derived neurotoxin
  - d. eosinophil peroxidase
  
6. Which of the following lipid mediators is the predominant metabolite of the 5-lipoxygenase pathway, generated by eosinophils?
  - a. LTB<sub>4</sub>
  - b. LTC<sub>4</sub>
  - c. LTD<sub>4</sub>
  - d. LTE<sub>4</sub>
  
7. Monoclonal anti-IL-5 therapies for asthma exert several effects on the biology of eosinophils. Which of the following eosinophil-derived substances induces tissue damage and remodeling?
  - a. LTC<sub>4</sub>
  - b. RANTES and GM-CSF
  - c. TGF-beta and MMP-9
  - d. MBP, ECP, EDN, EPX
  
8. The most potent eosinophil chemo-attractants include platelet activating factor (PAF), LTD<sub>4</sub>, C5a and CCL11 (eotaxin-1) and CCL5 (RANTES). Which of the following is implicated in the pathogenesis of eosinophilic esophagitis?
  - a. PAF
  - b. LTD<sub>4</sub>
  - c. eotaxin-1
  - d. RANTES
  
9. Extracellular release of eosinophil granule contents is a major effector function, implicated in host defense and pathologic disease processes. Which of the following granule release forms involves granule fusion with the cell membrane, leading to sudden large increments in release?
  - a. sequential release
  - b. compound exocytosis
  - c. piecemeal degranulation
  - d. cytolysis
  
10. In addition to protection from helminths, eosinophils are purported to serve a role against certain viral infections. An increase in eosinophil number and concentration of eosinophil granule proteins can be found in the respiratory tracts of patients infected with this virus:
  - a. respiratory syncytial virus
  - b. adenovirus
  - c. rhinovirus
  - d. influenza A

**Answers:**

1. **b) Charcot-Leyden crystal protein** (page 265 and page 267). Primary granules contain Charcot-Leyden crystal protein. Secondary granules contain major basic protein, eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin. Small granules contain acid phosphatase and arylsulfatase. Secretory vesicles contain membrane-bound cytochrome b558, CD11b, albumin, and the alpha chain or beta-2 integrin.
2. **a) GATA-1** (page 265 and Figure 16-3). Production of eosinophils depends on different transcription factors including GATA-1, PU.1, and C/EBP members. PU.1 determines distinct cell lineage fates and GATA-1 and PU.1 synergistically induce eosinophil lineage differentiation. GATA-1 binding site deletion in mice has demonstrated a specific loss of eosinophils.
3. **b) IL-5 receptor and CCR3** (page 266). In the bone marrow, committed eosinophil precursors can be identified by their expression of IL-5 receptor and the chemokine receptor CCR3.
4. **d) evening** (page 266). Eosinophils exhibit diurnal variation. In the peripheral blood, the lowest levels are detected in the morning and the highest levels are seen in the evening.
5. **a) major basic protein** (page 268). Major basic protein has several roles; it disrupts *Schistosoma* membrane and is also toxic to *Trichinella*, *Trypanosoma*, *Staphylococcus aureus*, and *E. coli* as well as tumor cells. The concentration of MBP in the BAL fluid has been correlated with bronchial hyperreactivity in patients with asthma. MBP also increases airway responsiveness to inhaled methacholine. Eosinophil cationic protein has neurotoxic and antiviral properties. Eosinophil-derived neurotoxin is extremely neurotoxic; it also enhances Th2 responses through TLR-2 dependent mechanisms. Eosinophil peroxidase along with hydrogen peroxide and halide is anti-microbial against several pathogens.
6. **b) LTC<sub>4</sub>** (page 269). In eosinophils, the predominant metabolite of the 5-LO pathway is LTC<sub>4</sub>, which in turn, is metabolized to LTD<sub>4</sub> and LTE<sub>4</sub>. Eosinophils also produce large amounts of 5-HETE. Together, these mediators lead to contraction of smooth muscle airways, mucus secretion, and eosinophil and neutrophil infiltration into tissues.
7. **c) TGF-beta and MMP-9** (Figure 16-6). In the pathogenesis of asthma: MBP, ECP, EDN, and EPX induce epithelial injury, MMP-9 induces tissue damage and remodeling, LTC<sub>4</sub> results in smooth muscle airway contraction, GM-CSF and RANTES are cytokines/chemokines which enhance eosinophil recruitment and activation, and TGF-beta induces tissue remodeling and fibrosis. Anti-IL-5 therapies reduce the pathologic effects of these substances.
8. **c) eotaxin-1** (page 272-274). PAF is a potent and effective chemoattractant for eosinophils and also evokes the release of granule proteins from eosinophils. LTD<sub>4</sub> is a chemoattractant for eosinophils which can be blocked by CysLT1 antagonists.
9. **b) compound exocytosis** (page 274). Sequential release is seen *in vitro* and is demonstrated with a patch-clamp technique. Compound exocytosis results in sudden, large increments in capacitance which leads to individual granule fusion with the cell membrane. Piecemeal degradation involves numerous small vesicles budding off from larger granules and moving to the plasma membrane for fusion. Cytolysis is a not well understood mechanism.



10. **a) respiratory syncytial virus** (page 276). There are increased numbers of eosinophils and increased concentration of eosinophil granule proteins in the respiratory tracts of patients with RSV. In animal models infected with parainfluenza, treatment with anti-IL-5 and subsequent reduction in eosinophil levels lead to an increase in viral content in the airways.



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### Chapter 21: Pathophysiology of Allergic Inflammation

Prepared by: Melissa Gans, MD

1. Which of the following is released by epithelial cells to maintain mucosal mast cells at the airway and skin surface?
  - a. IL-9
  - b. Stem cell factor (SCF)
  - c. CCL17
  - d. CCL22
2. Th2 cells release all of the following cytokines except:
  - a. IL-4
  - b. IL-5
  - c. IL-9
  - d. IL-17
3. All of the following are true about TSLP except:
  - a. Epithelial cells and mast cells release TSLP.
  - b. TSLP acts on immature dendritic cells to mature.
  - c. TSLP directly acts on B lymphocytes and eosinophils.
  - d. TSLP stimulates the release of CCL17, which attracts Th2 cells via CCR4.
4. Why is measuring exhaled nitric oxide more useful as a marker of asthma than allergic rhinitis?
  - a. The local production of nitric oxide by the nasal mucosa is diluted as a consequence of the high nitric oxide production from paranasal sinuses.
  - b. Nitric oxide is not elevated in patients with allergic rhinitis.
  - c. Nitric oxide is not increased further during the late response to inhaled allergen.
  - d. There is not increased expression of inducible nitric oxide synthase in airway epithelial cells.
5. Which of the following does not lead to increased airway mucus secretion?
  - a. Stimulation by Th2 cytokines and oxidative stress.
  - b. Epidermal growth factor activation.
  - c. Inhibition of acetylcholine and substance P.
  - d. Increased expression of mucin gene MUC5AC.

6. In resting Th2 cells, GATA3 is localized to the cytoplasm. What causes phosphorylation of GATA3 so that GATA3 is imported to the nucleus and binds to the promoter region of Th2 cytokine genes to activate gene expression and cause allergic inflammation?
  - a. Interaction with antigen-presenting dendritic cells activates the T cell receptor (CD3) and costimulatory molecule CD28 causing p38 mitogen-activated protein kinase (MAPK) signal transduction.
  - b. Inflammatory stimuli activate enzyme IKK2 which degrades NF- $\kappa$ B inhibitor.
  - c. IL-4 and IL-13 stimulate Jak1 and Jak3 to phosphorylate STAT6.
  - d. IL-27 activates STAT1 and IL-12 activates TSAT4 which signals T-bet in Th1 cells.
7. Which of the following is inappropriately paired with the effect on airway smooth muscle by inflammatory cell mediators?
  - a. Contraction: histamine, cys-LT, kinin, prostanoid, endothelin
  - b. Proliferation: PDGF, EGF, endothelin-1
  - c. Secretion: cytokines, chemokines, prostanoids
  - d. Neurogenic inflammation: neurotrophin, SP, CGRP
8. Th17 cells release which of the following?
  - a. IL-2
  - b. IL-9
  - c. IFN- $\gamma$
  - d. IL-22
9. All of the following are major explanations for activating airway epithelial cells to promote inflammation in asthma through eosinophil survival and chemotaxis, lymphocyte activation, smooth muscle hyperplasia, and fibroblast activation except:
  - a. Viruses release oxygen and nitric oxide.
  - b. Basophils release histamine.
  - c. Allergens act on the Fc $\epsilon$ RII receptor.
  - d. Macrophages release TNF- $\alpha$ , IL-1 $\beta$ , and IL-6.
10. Which of the following is true regarding chemokines in the recruitment of inflammatory cells in allergic disease?
  - a. Chemokines do not act in sequence to determine the final inflammatory response so chemokine inhibitors will likely be very effective.
  - b. The only chemokines that are chemotactic for eosinophils are CCL11 and CCL24.
  - c. Chemokines work through G protein-coupled receptors.
  - d. The only chemokine receptor for allergic disease is CCR3.

**Answers:**

1. **B.** p. 328, Figure 21-2. Epithelial cells release stem cell factor to maintain mucosal mast cells. CCL17 and CCL22 are released by epithelial cells to act on CCR4 to attract Th2 cells. IL-9 is released by Th2 cells to stimulate mast cell proliferation.
2. **D.** p. 329, Figure 21-3. Th2 cells release IL-4, IL-5, IL-9, and IL-13. Th17 cells release IL-17 and IL-22.
3. **C.** p. 332, Figure 21-6. TSLP does not directly act on eosinophils and B lymphocytes. TSLP directly acts on Th2 cells which then release cytokines that acts on eosinophils and B lymphocytes.

4. **A.** p. 333. Nitric oxide is elevated in patients with allergic rhinitis. Nitric oxide is increased further during the late response to inhaled allergen. There is increased expression of inducible nitric oxide synthase in airway epithelial cells.
5. **C.** p. 335, Figure 21-8. Increased release of acetylcholine and substance P cause increased mucus hypersecretion. Epidermal growth factor causes increased expression of the mucin gene MUC5AC.
6. **A.** p. 337, Figure 21-11. When inflammatory stimuli activate enzyme IKK2 which degrades NF- $\kappa$ B inhibitor, NF- $\kappa$ B subunits translocate to the nucleus where they bind to promoter regions of inflammatory genes. When IL-4 and IL-13 stimulate Jak1 and Jak3 to phosphorylate STAT6, GATA3 is activated (but not specifically moved from the cytoplasm to the nucleus). When IL-27 activates STAT1 and IL-12 activates TSAT4 which signals T-bet in Th1 cells, Th1 cytokines are released – GATA3 actually works against this pathway.
7. **D.** p. 334-335, Figures 21-7, 21-9. Sensory nerves release S P and CGRP to act on inflammatory cells. Inflammatory cells release neurotrophins to act on sensory nerves.
8. **D.** p. 329, Figure 21-3. Th17 cells release IL-17 and IL-22. Th1 cells release IL-2 and IFN- $\gamma$ . Th9 cells release IL-9.
9. **B.** p. 331-330, Figure 21-4. Although basophils do release histamine, this is not believed to play a major role in asthma. Small increase in basophils has been documented in the airways of asthmatic patients, though these cells are far outnumbered by eosinophils.
10. **C.** p. 333. Chemokines do act in sequence in determining the final inflammatory response so inhibitors may not be effective, depending on the kinetics of the response. Examples of chemokines that are chemotactic for eosinophils include: CCL11, CCL24, CCL28, CCL5, and CCL13. CC3 and CC4 are chemokine receptors that can be targeted for their involvement in allergic disease.



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### Chapter 25: Resolution of Allergic Inflammation

Prepared by: Ohn Chow, MD

1. Which of the following is NOT a feature of apoptosis?
  - a. Extrusion of naked DNA into the extracellular environment
  - b. Extrusion of vesicles containing cellular components
  - c. Preservation of an intact cell membrane
  - d. Fragmentation of DNA (karyorrhexis)
2. Which cell type is thought to be primarily responsible for clearance of apoptotic cells?
  - a. Neutrophils
  - b. Macrophages
  - c. Eosinophils
  - d. Mast cells
3. Which of the following is NOT felt to be a feature of corticosteroids that contributes to their efficacy in resolution of allergic inflammation?
  - a. Inducing eosinophil apoptosis
  - b. Increased macrophage clearance of apoptotic cells
  - c. Increased production of interleukin-10
  - d. Increased production of TNF alpha
4. Mutations in which gene are found in the greatest percentage of patients with systemic mastocytosis?
  - a. *ASXL1*
  - b. *CBL*
  - c. *c-KIT*
  - d. *DNMT3A*
5. Which of the following lipid mediators is NOT considered to be anti-inflammatory?
  - a. Lipoxin A4
  - b. Leukotriene B4
  - c. Resolvin E1
  - d. Protectin D1
6. Which of the following is a NOT a potential adverse effect of corticosteroids?
  - a. Cataracts
  - b. Increased glucose tolerance
  - c. Osteoporosis
  - d. Avascular necrosis of the femoral head

7. What type of receptor is the glucocorticoid receptor?
  - a. G-protein coupled receptor
  - b. Receptor tyrosine kinase
  - c. Ligand-gated ion channel
  - d. Nuclear receptor
  
8. During apoptosis, which of the following directly results in release of cytochrome c into the cytoplasm?
  - a. Increased mitochondrial membrane permeability
  - b. Increased nuclear membrane permeability
  - c. Increased plasma membrane permeability
  - d. Increased lysosomal membrane permeability
  
9. Which of the following cytokines increases eosinophil apoptosis?
  - a. Interleukin-3
  - b. Interleukin-4
  - c. Interleukin-5
  - d. Interleukin-13
  
10. Activation of which of the following receptors leads to eosinophil apoptosis?
  - a. Interleukin-5 receptor
  - b. FAS ligand receptor
  - c. TRAIL
  - d. GM-CSF receptor

**Answers:**

1. **A.** Extrusion of naked DNA into the extracellular environment is a feature of “ETosis”, a form of cell death distinct from apoptosis which leads to the generation of extracellular traps. Apoptosis characterized by preservation of the cell membrane, and cellular components and fragmented DNA is packaged into extruded vesicles called apoptotic bodies.
2. **B.** Macrophages are the primary cells responsible for engulfment of apoptotic cells and apoptotic bodies.
3. **D.** Corticosteroids increase eosinophil apoptosis, clearance of apoptotic cells, and interleukin-10 production. Corticosteroids downregulate TNF-alpha, which likely contributes in part to their efficacy in a number of inflammatory conditions.
4. **C.** Although mutations in all of the genes listed above have been reported in patient with systemic mastocytosis, *c-KIT* mutations are by far the most common, specifically the D816V mutation.
5. **B.** Leukotriene B4. The remaining lipid mediators are considered to be anti-inflammatory and play a role in resolution of allergic inflammation.
6. **B.** Corticosteroids commonly lead to impaired glucose tolerance. The remaining adverse effects can be seen with corticosteroid use.

7. **D.** The glucocorticoid receptor is a nuclear receptor.
8. **A.** Cytochrome c is contained in the mitochondria. Certain pro-apoptotic proteins, such as BAX, can translocate into the mitochondria when activated, leading to increased mitochondrial membrane permeability and subsequent cytochrome c release.
9. **B.** Interleukin-4 notably increases eosinophil apoptosis, in contrast to most other Th2 cytokines.
10. **B.** Activation of the remaining receptors promotes eosinophil survival.



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### Chapter 35: Contact Dermatitis

Prepared by: Kristine Vanijcharoenkarn, MD

1. The weighted average prevalence of contact allergy to at least one contact allergen (based on data collected on all age groups and in all reporting countries between 1966-2007) is:
  - a. 15.9%
  - b. 19.5%
  - c. 35.9%
  - d. 41.5%
2. Fill in the blank: "Contact dermatitis occurred \_\_\_\_\_ as frequently in women as in men, and often started at a(n) \_\_\_\_\_ age, with a prevalence of 15% in \_\_\_\_\_ year-olds."
  - a. Half, young, 12-16
  - b. Half, older, 30-35
  - c. Twice, young, 12-16
  - d. Twice, older, 30-35
3. Acute contact dermatitis caused by chromium (VI) (CrVI) has long been a recognized occupational problem, especially from exposure to:
  - a. Hair dyes
  - b. Baking yeast
  - c. Mobile phones
  - d. Wet cement
4. Irritant contact dermatitis is the most common form of contact dermatitis in the population. An irritant will cause direct injury to the skin in any person, if applied in a sufficient concentration for a sufficient amount of time, without prior sensitization or immunological memory. Irritants include wet work. "Wet work" is defined when individuals have their skin exposed to liquids longer than:
  - a. 1 hrs/day, or use occlusive gloves longer than 1 hrs/day, or clean the hands very often (eg 10 times/day or less if cleaning procedure is aggressive)
  - b. 2 hrs/day, or use occlusive gloves longer than 2 hrs/day, or clean the hands very often (eg 20 times/day or less if cleaning procedure is aggressive)
  - c. 3 hrs/day, or use occlusive gloves longer than 3 hrs/day, or clean the hands very often (eg 30 times/day or less if cleaning procedure is aggressive)

- d. 4 hrs/day, or use occlusive gloves longer than 4 hrs/day, or clean the hands very often (eg 40 times/day or less if cleaning procedure is aggressive)
5. Topical agents causing phototoxic reactions particularly include plants containing furocoumarins, such as:
- Celery, carrot, and citrus fruits
  - Avocado, blueberries, strawberries
  - Spinach, red cabbage, brussels sprouts
  - Zucchini, cucumbers, squash
6. Which syndrome - a form of systemic contact dermatitis - can occur when sensitized persons are exposed to allergens from routes other than skin exposure, such as orally, intravenously, or by inhalation?
- Lemur syndrome
  - Rhinoceros syndrome
  - Hippopotamus syndrome
  - Baboon syndrome
7. Which pairing of allergen and common source of exposure is Incorrect?
- Thiuram mix – rubber accelerator
  - Carba mix – metal items, coins
  - p-Phenylenediamine – permanent hair dye
  - Quaternium 15 – preservative
8. Unlike in irritant contact dermatitis, the borders of the lesions in allergic contact dermatitis are \_\_\_\_\_ defined. In ACD, additional lesions \_\_\_\_\_ appear on other parts of the body that have not come into contact with the allergen.
- Well; can
  - Well; can't
  - Poorly; can
  - Poorly; can't
9. What has been proven effective in treating chronic contact dermatitis, particularly that affecting the hands?
- Mycophenolate Mofetil
  - Azathioprine
  - Laser therapy
  - Phototherapy
10. In irritant contact dermatitis of the hands, the predominant areas involved include:
- the web spaces initially, the dorsal aspects of the hands and fingers
  - the palmar areas of the hands initially
  - the wrist areas
  - the fingernails initially, then the knuckles of the fingers

**Answers:**

1. **b**, pg. 566 – The weighted average prevalence of contact allergy to at least one contact allergen is 19.5%
2. **c**, pg. 566 – Contact dermatitis occurred twice as frequently in women as in men, and often started at a young age, with a prevalence of 15% in 12-16-year-olds.
3. **d**, pg. 566 – During the construction of the Channel tunnel connecting continental Europe with Britain, the prevalence of chromate allergy in cement workers was reported to be as high as 17%. Subsequently, the EU regulated the content of chromium in cement, and sensitization to chromate in construction works has since declined. No such legislation exists in the United States. Other sources of chromate exposure include contact with leather tanned with salts containing chromate and this has become increasingly recognized.
4. **b**, pg. 567- According to the German regulation of hazardous substances at the workplace, “wet work” is defined when individuals have their skin exposed to liquids longer than 2 hrs/day, or use occlusive gloves longer than 2 hrs/day, or clean the hands very often (eg 20 times/day or less if cleaning procedure is aggressive)
5. **a**, pg. 567 - Topical agents causing phototoxic reactions particularly include plants containing furocoumarins, such as celery, carrot, and citrus fruits.
6. **d**, pg. 568 – Systemic contact dermatitis may occur when sensitized persons are exposed to allergens from routes other than skin exposure, such as orally, intravenously, or by inhalation. Clinical manifestations may include flare-ups of dermatitis in previous sites or of positive patch test site reactions, as well as vesicular hand eczema and “baboon syndrome,” which refers to a well-demarcated rash on the buttocks, genital area, and thighs. Causes commonly include metals such as nickel, cobalt, chromate, gold, and mercury. In certain case, treatment includes dietary avoidance of the particular metal.
7. **b**, pg. 567 – Carba mix - the common source of exposure is rubber accelerators (p. 567 has a nice table)
8. **c**, pg. 568 - Unlike in irritant contact dermatitis, the borders of the lesions in allergic contact dermatitis are poorly defined. In ACD, additional lesions can appear on other parts of the body that have not come into contact with the allergen (a phenomenon known as secondary spread).
9. **d**, pg. 572 – In chronic contact dermatitis, particularly affecting the hands, phototherapy has proved effective. Currently, therapy mainly consists of either UVB light or psoralens plus UVA light (PUVA) applied topically or in a bath. With long-term therapy, the potential carcinogenic risk must be considered.
10. **a**, pg. 568 – It often is not possible to distinguish the clinical findings in ICD from those in ACD. Classically, the first signs of ICD are dry and slightly scaly skin, with increasing redness and lichenification after prolonged or repeated exposure to an irritant(s). This may be followed by formation of fissures, also known as rhagades. Itching is generally not as severe as in ACD. On the hands, the predominant areas involved include the web spaces initially, the dorsal aspects of the



hands and fingers, as well as exposed portions of the forearms. Over the course of disease, the palms may also be involved. The eczematous lesions generally remain limited to exposure sites, and secondary spread to other areas typically does not occur. This feature often is useful to differentiate ICD from ACD.



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### Chapter 62: Immunologic Nonasthmatic Diseases of the Lung

Prepared by: Ekta Kakkar, MD

1. In granulomatosis with polyangiitis, which pattern of cytokine production is increased in response to environmental stimuli and contribute to granuloma formation?
  - a. Th1 cytokines
  - b. Th2 cytokines
  - c. Th1 and Th2 cytokines
  - d. Th1 and Th17 cytokines
2. Tissue biopsy of an affected organ in which condition would show absence of granuloma formation?
  - a. Hypersensitivity pneumonitis
  - b. Churg-Strauss syndrome
  - c. Microscopic polyangiitis
  - d. Histoplasmosis
3. A 50-year-old Caucasian male with vasculitis is diagnosed with mononeuritis multiplex. Which of the following is most likely to be true?
  - a. He has asthma and a high eosinophil count.
  - b. He has upper and lower airway involvement as well as glomerulonephritis.
  - c. He has bilateral hilar lymphadenopathy.
  - d. He will likely develop diffuse alveolar hemorrhage.
4. A 45-year-old female is diagnosed with granulomatosis with polyangiitis. She is found to have a positive ANCA. The ANCA can be used in this condition for what purpose?
  - a. A positive ANCA is diagnostic for granulomatosis with polyangiitis.
  - b. ANCA titers do not correlate well with the disease.
  - c. ANCA titers can be used to evaluate disease severity.
  - d. ANCA titers can be used to determine a relapse in disease.
5. Which of the following disorders is associated with an increased genetic predisposition?
  - a. Goodpasture's syndrome
  - b. Microscopic polyangiitis
  - c. Churg-Strauss syndrome
  - d. Sarcoidosis

6. The following CXR is consistent with which stage of sarcoidosis?



- a. Stage 0
- b. Stage I
- c. Stage II
- d. Stage III
- e. Stage IV

7. In which of the following conditions is plasmapheresis a first-line therapy?

- a. Granulomatosis with polyangiitis
- b. Serum sickness
- c. Goodpasture's syndrome
- d. Myasthenia Gravis

8. A 45-year-old woman is found to have vasculitis, and her anti-proteinase 3 antibody is positive. Which of the following conditions does she most likely have?

- a. Churg-Strauss syndrome
- b. Microscopic polyangiitis
- c. Polyarteritis nodosa
- d. Granulomatosis with polyangiitis

9. A 38-year-old African American woman is found to have bilateral hilar lymphadenopathy with parenchymal infiltrates on CXR. She is scheduled to have a bronchoscopy. What will be true about her biopsies and bronchoalveolar lavage (BAL)?

- a. Pathology will show caseating granulomas
- b. BAL will show an elevated CD4 to CD8 ratio
- c. BAL will show a decreased CD4 to CD8 ratio
- d. BAL will show elevated neutrophils

10. What contributes to development of fibrosis in sarcoidosis?

- a. Shift from a Th1 response to a Th2 response
- b. Shift from a Th2 response to a Th1 response
- c. Downregulation of a Th1 response
- d. Downregulation of a Th2 response

**Answers:**

1. **d.** Page 1015. Patients with granulomatosis with polyangiitis have an immune defect that leads to excessive production of Th1/Th17 cytokines (IL-17, TNF, and IFN- $\gamma$ ).
2. **c.** Page 1019. Absence of granulomatous inflammation in microscopic polyangiitis helps to differentiate it from other small vessel vasculitides discussed in this chapter.
3. **a.** Page 1020. Mononeuritis multiplex is the most common extrapulmonary manifestation of Churg-Strauss Syndrome which is characterized by asthma, allergic granulomatosis, and vasculitis. The characteristic laboratory finding in patients with Churg-Strauss Syndrome is peripheral eosinophilia.
4. **b.** Page 1015. ANCA antibody titers do not correlate well with disease activity, and patients in remission can continue to have a high ANCA titer.
5. **d.** Page 1021. There is an increased risk of sarcoidosis among first-degree relatives of patients with sarcoidosis. Siblings have a relative risk of 5.8 of having the disorder.
6. **b.** Page 1023. Stage 0 indicates no visible abnormalities. Stage I indicates bilateral hilar lymphadenopathy without parenchymal abnormalities. Stage II is bilateral hilar lymphadenopathy with pulmonary parenchymal abnormalities. Stage III is parenchymal infiltrates without hilar adenopathy, and Stage IV is pulmonary fibrosis.
7. **c.** Page 1028. Therapy for Goodpasture's syndrome consists of prednisone, oral cyclophosphamide, and plasmapheresis daily for 14 days.
8. **d.** Page 1017. Antiproteinase-3 ANCA is positive in 75-90% of granulomatosis with polyangiitis patients. It is positive in 10-50% of patients with microscopic polyangiitis and <5% of patients with Churg-Strauss Syndrome.
9. **b.** Page 1022. This patient has sarcoidosis in which BAL shows increased lymphocytes and macrophages and an increased CD4/CD8 ratio. Pathology will show noncaseating granulomas.
10. **c.** Figure 62-4, page 1025. Release of TGF- $\beta$  and CCL10 as well as downregulation of the Th1 response leads to fibrosis. In the initial phase of sarcoidosis, there is an increase in Th1 cytokine production and CD4+ T cell activation.



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### Chapter 75: Eosinophilia and Eosinophil-Related Disorders

Prepared by: Anita Sivam, DO, University of Tennessee Health Science Center

1. Which of the following stimulate differentiation, maturation, and activation of eosinophils?
  - a. IL-3, IL-4, IL-13
  - b. IL-4, IL-5, IL-13
  - c. GM-CSF, IL-3, IL-4
  - d. GM-CSF, IL-3, IL-5
  - e. GM-CSF, IL-3, IL-13
2. 65-year-old male with history of intermittent asthma and chronic rhinosinusitis who was vacationing in Brazil has bilateral arm and leg numbness for one day. Physical exam shows wheezing and hyperreflexia of lower extremities. Labs show eosinophil count of 8260/mL. What is the best course of action?
  - a. Echocardiogram, troponin, CBC, CMP
  - b. Imatinib 400 mg
  - c. Prednisone 1 mg/kg
  - d. Prednisone 1 mg/kg and ivermectin
3. Which diagnosis is most consistent with a clinical picture that includes recurrent sinopulmonary infections, persistent cutaneous viral infections and elevated IgE:
  - a. DOCK8 deficiency
  - b. Job's syndrome
  - c. NADPH oxidase deficiency
  - d. Wiskott Aldrich syndrome
4. A 29-year-old male comes into the office with complains of chronic rhinitis. A nasal smear is done and shows marked eosinophilia. A skin test is performed and is negative. Patient does not have a history of asthma or aspirin sensitivity. What is this history suggestive of?
  - a. Chronic sinusitis with nasal polyps
  - b. Chronic sinusitis without nasal polyps
  - c. Nonallergic rhinitis with eosinophilia syndrome
  - d. Allergic rhinitis
  - e. Atrophic rhinitis

5. A 14-year-old male with history of acne being treated with minocycline is brought to the emergency department for evaluation of acute worsening of facial, hand, and lower extremity edema. He has some subjective fevers and chills. Temperature is 38.2 C. On physical examination, you notice prominent facial edema and morbilliform eruption. Lab results show elevated LFTs and creatinine. Absolute eosinophil count is 2500/mL. What is a proposed mechanism that has been implicated in this diagnosis?
  - a. Sequential reactivation of herpes viruses
  - b. Genetic mutations in cytochrome p350 system
  - c. Concurrent alcohol use with minocycline
  - d. Undiagnosed immunodeficiency
  
6. What do primary granules of eosinophils contain?
  - a. Major basic protein
  - b. Eosinophil cationic protein
  - c. Eosinophil peroxidase
  - d. Charcot-Leyden crystals
  - e. Eosinophil-derived neurotoxin
  
7. Which of the following chemokines help eosinophils migrate to the tissue?
  - a. CCL-4
  - b. CCL-5
  - c. CXCL-8
  - d. CCL-10
  - e. CCL-13
  
8. A 68-year-old female with increased urinary frequency and dysuria is diagnosed with a urinary tract infection and treated with antibiotics. About 10 days later, she develops a dry hacking cough and dyspnea. She is noted to have crackles on examination. HSCT shows diffuse fine glass ground infiltrates. Peripheral blood eosinophil count is 1480/mL. What medication is suspected to cause eosinophilia and pulmonary infiltrates in this scenario?
  - a. Ciprofloxacin
  - b. Bactrim
  - c. Nitrofurantoin
  - d. Penicillin
  
9. A 28-year-old medical student recently returned from Kenya from a medical missions trip. She complains of pruritic rash for two months. Physical exam shows diffuse urticarial as well as a salmon-colored serpiginous lesion on her lower right back. Screening labs are drawn and show an absolute eosinophil count of 3500/mL. What is the most likely diagnosis?
  - a. Cutaneous larva
  - b. Strongyloidiasis
  - c. Idiopathic hypereosinophilic syndrome
  - d. Ascaris

10. A 72-year-old male with hepatosplenomegaly and petechiae is found to have increased anemia, thrombocytopenia, and increased serum B12 and tryptase. Patient is found to have deletion of 4q12. What should he be treated with?
- Imatinib
  - Nothing, repeat labs in 3 months
  - Methylprednisolone
  - Benralizumab

**Answers:**

- D.** Page 1205. The three eosinophil growth factor cytokines are granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5.
- D.** Page 1212, 1218. This is the clinical picture of eosinophilic granulomatosis with polyangiitis (EGPA), now with neurologic involvement. Because the patient is having neurologic involvement, treatment must be started immediately, even before continuing workup. Treatment includes prednisone 1 mg/kg. However, ivermectin should be added to prevent disseminated strongyloidiasis due to the steroids. Imatinib is not effective in EGPA.
- A.** Page 1219. DOCK8 deficiency is an autosomal recessive form of Hyper-IgE syndrome. Clinical characteristics include viral skin infections with severe and difficult to treat HPV, HSV, VZV, and molluscum contagiosum. Patients can have pneumonias but no pneumatoceles (contrast to Job's syndrome). Therapy includes IVIG and HSCT.
- C.** Page 1206. Nasal eosinophilia and sometimes blood eosinophilia are characteristic of nonallergic rhinitis with eosinophilia syndrome (NARES). These patients have nasal eosinophilia but have negative allergic histories, negative skin test results, normal IgE levels, normal bronchial responsiveness and no aspirin sensitivity.
- A.** Page 1208. This is DRESS due to minocycline use. Mechanisms that have been implicated in DRESS syndrome include drug detoxification enzyme abnormalities with subsequent accumulation of reactive drug metabolites, sequential reactivation of herpesviruses, such as cytomegalovirus, Epstein-Barr virus, human herpesvirus-6 and -7, and genetic predisposition associated with certain human leukocyte antigen alleles.
- D.** Review book, page 82. Primary granules contain Charcot-Leyden crystals. Secondary granules contain major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin.
- B.** Review book, page 82. CCL-5 is also known as RANTES. Eotaxin (also known as eotaxin-1, CCL-11; eotaxin-2, CCL-24) is also a chemokine involved in helping eosinophils migrate to tissue.

8. **C.** Page 1207. Useful article: [https://www.jacionline.org/article/S0091-6749\(10\)00660-3/pdf](https://www.jacionline.org/article/S0091-6749(10)00660-3/pdf). Diverse agents can stimulate pulmonary eosinophilia. Symptoms including dyspnea, weight loss, cough, chest pain, and fever may appear acutely after ingestion. When rechallenged, pulmonary symptoms frequently recur within 48 hours, and infiltrates may develop in the same locations as the original infiltrates.
9. **B.** Page 1208. Although idiopathic HES is a possibility, given the travel history and the characteristic skin lesion (“larva currens”), strongyloidiasis is the most likely diagnosis. The lesions of cutaneous larva migrans are intensely pruritic, raised, and typically occur on the feet or other exposed areas. Whereas the dermatologic manifestations of drug eruption can be extremely varied and include urticaria, no medication history is given and a serpiginous lesion would be extraordinarily unusual.
10. **A.** This patient has HES with myeloproliferative features should be treated first line with tyrosine kinase inhibitor imatinib. Those with cardiac injury should be treated with prednisone at the same.



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### Chapter 79: Drug Allergy

Prepared by: Nilamben D Patel, DO, Boston Medical Science Center

1. What are examples of Type A and Type B reactions?
  - a. Type A: Nausea from antibiotics, Type B: hepatic failure from acetaminophen
  - b. Type A: headache from methylxanthines, Type B: anaphylaxis from beta lactams
  - c. Type A: G6PD associated anemia, Type B: tinnitus from aspirin
  - d. Type A: reaction after radiocontrast media, Type B: G6PD associated anemia
2. Which is the immunodominant epitope (major determinant) of penicillin?
  - a. Penicilloyl epitope
  - b. Penicillenic acid
  - c. Penicillin
  - d. Pen G
3. Minor determinants of penicillin are associated most commonly with what type of reactions?
  - a. Urticaria
  - b. AGEP
  - c. DRESS
  - d. Serum sickness
  - e. Anaphylaxis
4. P-i mechanism explains for which of the following bizarre phenomenon?
  - a. Delayed onset drug allergy
  - b. Toxic epidermal necrolysis
  - c. First encounter drug hypersensitivity
  - d. Erythema multiforme
5. Type IVa reactions involve the secretion of large amounts of which cytokine?
  - a. IL – 5
  - b. IFN –  $\gamma$
  - c. IL – 13
  - d. CXCL8
  - e. IL – 4

6. Type IVc reactions activate cytotoxic T cells in which conditions?
  - a. Hemolytic anemia
  - b. Acute urticarial
  - c. AGEP
  - d. Contact dermatitis
  - e. PPD (tuberculin skin test)
  - f. Maculopapular exanthema with eosinophilia
  
7. Patients requiring taxanes can be treated for infusion reactions with which of the following?
  - a. Increasing rate of infusion
  - b. Increased rate of infusion, antihistamines, corticosteroids
  - c. Decreasing the rate of infusion
  - d. Decreasing the rate of infusion, antihistamines, corticosteroids
  
8. The definitive diagnosis of drug allergy involves...
  - a. Skin prick testing
  - b. Skin prick testing and intradermal testing
  - c. Provocative drug testing
  - d. Lymphocyte activation test
  - e. Patch testing
  
9. How long should skin testing be delayed after an acute anaphylactic episode?
  - a. No delay
  - b. 4 weeks
  - c. 3 months
  - d. 6 months
  - e. 12 months
  
10. Patients with a history of severe anaphylaxis the initial dose for drug sensitization should be?
  - a. Between 1/1,000,000 and 1/10,000
  - b. Between 1/10,000 and 1/100
  - c. Between 1/10,000 and 1/1,000
  - d. Between 1/1,000,000 and 1/1,000

**Answers:**

1. **B.** Table 79 – 1. Pg 1275. Type A reactions are reactions that occur in most normal patients when given a sufficient dose. They are predictable from known pharmacologic properties. Type B reactions are unpredictable or unexpected restricted to a vulnerable population.
2. **A.** Figure 79 – 2. Pg 1276. The major determinant AKA the immunodominant epitope of penicillin is the Penicilloyl.
3. **E.** pg 1276. The minor determinants of penicillin are of major clinical importance because they are generally associated with anaphylaxis.
4. **C.** Pg 1276. The P-i concept by Pichler and colleagues described the direct pharmacologic interaction of drugs with immune receptors. A chemically inert drug that is unable to covalently bind to peptides or proteins may activate the immune system by directing binding and reversibly to HLA molecules on APCs or TCRs on certain T cells.
5. **B.** Figure 79-7. Page 1281. Type IVa reactions involve Th1 type immune reaction that activates macrophages resulting in large amounts of IFN –  $\gamma$
6. **C.** Page 1282. Type IVd reactions are neutrophilic inflammation dominant resulting in AGEP, Bechet's disease
7. **D.** Page 1284. Taxanes can lead to mast cell degranulation by nonimmune mechanisms. Such infusions are common with the first immune. Slowing the infusion and pretreatment with antihistamines, steroids can prevent hypersensitivity reactions.
8. **C.** Page 1287. Intradermal and prick skin testing are one method of diagnosing drug allergies however the MOST definitive way is provocative drug challenge. Patients are given gradually increasing doses of the drug. Provocative drug tests should be done if there was a reaction within 4 – 6 weeks, patient used anti – histamines, steroids or has an underlying uncontrolled conditions (urticaria, asthma, URI, etc.).
9. **B.** Page 1288. Skin testing should be delayed by 4 weeks to avoid the refractory period and false negative testing.
10. **A.** Page 1289. Desensitization protocols for patients with severe anaphylaxis (hypotension, loss of consciousness, severe bronchospasm, etc.) should be started at a lower concentration than patients with milder symptoms.



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### Chapter 81: Reactions to Foods

Prepared by: Ruchi Singla, MD, Ohio State University

1. Which of the following allergens is most responsible for clinical reactivity to egg in egg-allergic children?
  - a. ovalbumin
  - b. ovomucoid
  - c. ovotransferrin
  - d. ovomglobulin
2. What percentage of children with milk allergy typically tolerate extensively heated milk in baked products?
  - a. 25%
  - b. 50%
  - c. 66%
  - d. 75%
3. There is high cross-reactivity between cow's milk proteins with milk from which of the following animals:
  - a. lamb
  - b. horse
  - c. camel
  - d. goat
4. Which of the following allergens has been identified as a major allergen in adults with pollen allergy and oral allergy symptoms to peanuts?
  - a. Ara h 1
  - b. Ara h 2
  - c. Ara h 6
  - d. Ara h 8
5. Which of the following cell types peaks 4-6 hours after the onset of a food protein-induced enterocolitis syndrome reaction?
  - a. Peripheral blood eosinophils
  - b. Lung eosinophils
  - c. Peripheral blood neutrophils
  - d. Lung mast cells

Supported by:

6. While of the following statements is most accurate regarding food-dependent, exercise-induced anaphylaxis (FDEIA):
  - a. Symptoms occur 4-6 hours after exercise following food ingestion.
  - b. This disorder is more common in males than females.
  - c. In the absence of exercise, patients can typically ingest the trigger food without reaction.
  - d. This disorder appears to be most prevalent in early 40s.
  
7. Which of the following pairs of vaccines are contraindicated in persons with history of urticarial, angioedema, asthma or anaphylaxis to egg proteins?
  - a. Yellow fever and MMR
  - b. Yellow fever and rabies
  - c. DTaP and influenza
  - d. Rabies and typhoid
  
8. How long does it typically take for cow's milk and soy protein-induced proctocolitis to resolve after allergen avoidance?
  - a. 3 – 6 months
  - b. 6 months – 12 months
  - c. 6 months – 2 years
  - d. 12 months – 2 years
  
9. Diagnosis of eosinophilic esophagitis depends on esophageal biopsy demonstrating eosinophilic infiltration with typically more than how many eosinophils per high-power field?
  - a. 10
  - b. 15
  - c. 20
  - d. 25
  
10. Heiner syndrome, a rare condition resulting in food-induced pulmonary hemosiderosis is most often associated with which food?
  - a. Beef
  - b. Milk
  - c. Egg
  - d. Wheat

**Answers:**

1. **b** – pg 1318. Egg white is considered more allergenic than the yolk, and ovomucoid (Gal d 1) is the dominant allergen in purified egg white protein. Blinded OFCs with ovomucoid-depleted egg white demonstrated that ovomucoid was responsible for clinical reactivity in most egg-allergic children.
2. **d** – pg 1317. About 75% of children with milk allergy tolerate baked milk.
3. **d** – pg 1317. Oral challenge studies indicate that at least 90% of cow's milk-allergic children react to goat's milk.
4. **d** – pg 1318. Ara h 8 is a Bet v 1 cross-reactive protein with low stability during roasting and no stability in gastric digestion. It has been identified as a major allergen in adults with pollen allergy and oral allergy symptoms to peanut.
5. **c** – pg 1325. After an acute Food Protein-Induced Enterocolitis Syndrome (FPIES) reaction, there is a prominent increase in the number of peripheral blood neutrophils, peaking at 4-6 hours from the onset of symptoms.
6. **c** – pg 1329. Food-Dependent, Exercise-Induced Anaphylaxis (FDEIA) occurs only when the patient exercises within 2-4 hours of ingesting food, but in the absence of exercise, the patient can ingest the food without any apparent reaction. This disorder appears to be more common in females than males, with highest prevalence in the late teens to mid-30s.
7. **b** – table 81-9, pg 1331. According to the National Institute of Allergy and Infectious Diseases (NIAID) sponsored clinical guideline for the diagnosis and management of food allergy in the United States, yellow fever and rabies vaccines are contraindicated in persons with history of urticaria, angioedema, asthma or anaphylaxis to egg proteins.
8. **c** – pg 1325. Cow's milk and soy protein-induced proctocolitis generally resolve within 6 months to 2 years of allergen avoidance, though refractory cases may be seen.
9. **b** – pg 1324. Diagnosis of eosinophilic esophagitis depends on esophageal biopsy demonstrating eosinophilic infiltration, typically more than 15 eosinophils per high-power field.
10. **b** – pg 1329. Food-induced pulmonary hemosiderosis or Heiner syndrome, is a rare condition characterized by recurrent pneumonia associated with pulmonary infiltrates and hemorrhage, hemosiderosis, gastrointestinal blood loss, iron-deficiency anemia and failure to thrive. Heiner syndrome is most often associated with a non-IgE mediated hypersensitivity to cow's milk, though reactions to egg, pork and buckwheat have also been reported.



Welcome to the FIT Board Review Corner, prepared by Timothy Chow, MD and Christopher Foster, MD, senior and junior representatives of the College'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 80:** Hypersensitivity to Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs  
Prepared by: Rebecca Koransky, MD

1. Aspirin Exacerbated Respiratory Disease (AERD) describes a clinical syndrome with three features - the "ASA triad." Which of the following choices below is not included in this triad?
  - a. Chronic rhinosinusitis with polyps
  - b. Asthma
  - c. Increased pulmonary infections
  - d. Hypersensitivity reactions to aspirin and other cross-reacting NSAIDs
  
2. Large amounts of infiltrates of what cell are most often found in the upper and lower airway mucosa of patients with AERD?
  - a. Neutrophils
  - b. Lymphocytes
  - c. Macrophages
  - d. Eosinophils
  
3. Patients with AERD have abnormal arachidonic acid metabolism. Which of the following is seen in patients with AERD?
  - a. Decreased production of Prostaglandin E2
  - b. Decreased production of leukotrienes
  - c. Decreased production of lipoxin A4
  - d. Increased production of all anti-inflammatory prostaglandins
  
4. What allele has been identified as a genetic marker for AERD in Polish and Korean populations?
  - a. HLA DQB1\*0301
  - b. HLA DPB1\*0301
  - c. HLA DRB1\*0301
  - d. HLA AB1\*0301

Supported by:



5. AERD develops in a distinctive pattern. What is the usual order of symptom development?
  - a. Rhinosinusitis with polyps, asthma, aspirin hypersensitivity
  - b. Aspirin allergy, rhinosinusitis with polyps, asthma
  - c. Asthma, aspirin allergy, rhinosinusitis with polyps
  - d. Aspirin allergy, asthma, rhinosinusitis with polyps
  
6. How do you definitively diagnosis AERD?
  - a. Clear history of adverse reaction to aspirin
  - b. Improvement of asthma when stopping aspirin
  - c. Identifying nasal polyps in at risk patients on exam
  - d. Aspirin provocation challenges
  
7. Aspirin desensitization can be used a treatment option for some patients. Desensitization to which dose of aspirin is recommended to maintain cross-desensitization to any dose of all NSAIDs?
  - a. 81mg
  - b. 162mg
  - c. 325mg
  - d. 650mg
  
8. Which NSAID hypersensitivity likely involves COX-1 inhibition?
  - a. Fixed drug eruption
  - b. Multiple NSAID induced urticaria
  - c. Single drug induced urticaria
  - d. Single drug induced anaphylaxis
  
9. A patient presents with urticaria to multiple NSAIDs. What is the next step in management?
  - a. Oral challenge with non-COX-1 inhibitor
  - b. Confirmatory oral challenge with COX-1 inhibitor
  - c. Desensitization to preferred NSAID
  - d. Avoid all NSAIDs
  
10. A patient presents with angioedema to a single NSAID. What is the next step in management?
  - a. Oral challenge test with chemically unrelated NSAID
  - b. Confirmatory oral challenge with same NSAID
  - c. Oral challenge with non-COX-1 inhibitor
  - d. Desensitization

**Answers:**

1. **C.** Page 1296. Patients with AERD, or Samter disease, usually present with chronic rhinosinusitis with polyps, moderate to severe asthma, and hypersensitivity reactions to aspirin and other cross-reacting NSAIDs.
2. **D.** Page 1298, 1301. The pathogenesis of AERD includes development of chronic inflammation of the upper and lower airway mucosa. Abundant amounts of eosinophils are found in mucosa of patients with AERD.
3. **A.** Page 1298. Abnormalities of arachidonic acid in patients with AERD include decreased prostaglandin E2 (PGE2 is anti-inflammatory), overproduction of leukotrienes, and increased production of lipoxin A4.
4. **B.** Page 1299. This allele was identified in studies of a Polish and Korean population. Patients with this allele showed lower FEV1 and high prevalence of rhinosinusitis with nasal polyps.
5. **A.** Page 1301. Nasal symptoms usually start by middle age and asthma develops a few years later. Aspirin hypersensitivity develops last - usually manifested as bronchospasm, rhinitis, and ocular injection.
6. **D.** Page 1301. "The diagnosis of AERD can be definitively established only through aspirin-provocation challenges". Challenges can be oral, inhaled, nasal, or IV. Controlled oral challenge with aspirin is the gold standard.
7. **C.** Page 1304. The target dose of desensitization depends on the diseases underlying the aspirin desensitization. The target dose for cardiovascular disease prevention is 81mg, the target dose to maintain cross-desensitization to all NSAIDs is 325mg, and the target dose for AERD patients is 650mg twice daily.
8. **B.** p. 1297, Table 80-1. Cox-1 inhibition is the likely mechanism in urticaria/angioedema induced by multiple NSAIDs. Single drug induced urticaria and anaphylaxis are IgE mediated. A fixed drug eruption is a form of delayed type hypersensitivity.
9. **B.** p. 1306, Figure 80-3. The first step is a confirmatory oral challenge with a COX-1 inhibitor. If positive, then an oral challenge with a non-COX-1 inhibitor should be done next.
10. **A.** p. 1306, Figure 80-3. The first step is an oral challenge test with a chemically unrelated NSAID. If positive, patient should be treated as a reactor to multiple NSAIDs.