Allergy and Immunology Board Review Corner: 2017

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FIT Board Review Corner – January 2017

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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 32 (pages 508-517): Effect of the Food Matrix and Processing on the Allergenic Activity of Foods
Prepared by Malika Gupta, MD, The Children’s Hospital of Philadelphia

1. Which of the following food processing methods lead to an increase in the allergenic potential of the food?
   a. Canning of fish.
   b. Baking of milk.
   c. Baking of egg.
   d. Boiling of shrimp.

2. Which of the following is true regarding Bet v 1 and related food allergies?
   a. Bet v 1 homologs in plant-derived foods are generally thermolabile.
   b. Individuals with birch pollen-related fruit allergies may tolerate stored fruit but not freshly picked fruit.
   c. Individuals with Bet v 1-related fruit allergies cannot consume pureed fruit products.
   d. Individuals with Bet v 1-related food allergies cannot tolerate ultrahigh temperature processed fruit products.

3. Which of the following about lipid transfer protein (LTP) associated fruit allergens is true?
   a. Expression of LTP allergens is upregulated during storage.
   b. Peeling fruits can make them safe for consumption by certain individuals with LTP allergies.
   c. Preparation of pasteurized, ultrahigh temperature treated fruit juices is sufficient to make them safe for individuals with LTP fruit allergies.
   d. Fruit purees and fresh juices don’t trigger reactions in individuals with LTP fruit allergies.

4. Lipocalins are a class of inhalant allergens. Which of the following lipocalins is a food allergen in cow’s milk protein?
   a. Bos d 2
b. Bos d 3  
c. Bos d 4  
d. Bos d 5

5. Allergy to celery spice is associated with sensitization to which Bet v 1 homolog?  
   a. Api g 1  
   b. Arah2  
   c. Bos d 4  
   d. Met e 1

6. Which is of the following statements is true regarding fining agents added to alcoholic beverages?  
   a. Certain alcoholic beverages contain residual levels of fining agents based on fish gelatin, milk casein or egg albumin.  
   b. Fining agents and their residues are made up of raw, unprocessed foods.  
   c. Individuals with allergies to fish and egg cannot react to alcoholic beverages when they are used as fining agents.  
   d. Reactions to fining agents are common.

7. Which of the following statements is true regarding oil refining?  
   a. Proteins are removed during the refining process, and highly-refined oils contain very low levels of residual protein.  
   b. Highly-refined soybean oils are not considered safe for consumption by individuals with soy allergies in Europe.  
   c. Highly-refined peanut oils have an EU labeling derogation.  
   d. Most of the protein is still retained during oil refining.

8. Which of the following statements is true with regards to the roasting and frying of peanuts?  
   a. Prolamin superfamily 2s albumin allergens lose their native structure after roasting and frying.  
   b. Maillard modification of allergens can add to allergenicity with roasting and frying.  
   c. Some cupin allergens become soluble with roasting.  
   d. Peanuts lose their allergenicity upon roasting.

9. Which of the following statements is true of conformational and linear epitopes of food allergens?  
   a. Linear epitopes are formed from segments of a polypeptide chain brought together by protein folding.  
   b. Conformational epitopes comprise short regions of 8-15 amino acids which tend to adopt a secondary structure.
c. Linear epitopes are unstable in response to food processing.
d. Food processing procedures may affect the way in which proteins are folded and can either destroy conformational epitopes or reveal new epitopes previously hidden by protein folding.

10. Which of the following processes increases the allergenicity of foods?
   a. Acid-treated gluten
   b. Baking of eggs
   c. Baking milk
   d. Cooking fruits and vegetables

**Answers**

1. D.
Tropomyosin is a well-studied allergen in crustacean and molluscan shellfish. Tropomyosin from the greasy back shrimp (Met e 1) is a heat-stable allergen and is found in many crustacean species. Boiling can enhance the allergenicity for some individuals. Therefore, boiled shrimp extracts can be used for diagnosis. The other three processes mentioned reduce (although do not abolish) allergenic activity of the listed foods.

2. A.
“Bet v 1 homologs in plant derived foods are generally thermolabile. This is why individuals with birch pollen-fruit allergy syndrome can usually eat cooked fruits and vegetables without experiencing the symptoms they have when eating fresh produce.

Individuals with birch pollen-related fruit allergies may be able to tolerate freshly picked fruit but not stored fruit. Individuals with Bet v 1 related fruit allergies usually can consume pureed fruit products. Individuals with Bet v 1-related food allergies usually can tolerate ultrahigh temperature processed fruit products.”

3. B.
“Removal of outer layers by physical or chemical peeling leads to loss of LTPs located in the outer layer. Thus, peeling fruits makes them safe for consumption by certain individuals with LTP allergies.

Expression of lipid transfer protein (LTP) allergens is downregulated during storage. Levels are higher in fresh fruits and decreased with storage but that still does not necessarily make these fruits safe for consumption. Preparation of pasteurized, ultrahigh temperature treated fruit juices is NOT sufficient to make them safe for individuals with LTP fruit allergies as the fruit LTPs retain a native-like structure. For this reason, fruit purees and fresh juices CAN trigger reactions in individuals with LTP fruit allergies.”
4. D.
“The only member of the lipocalin class that is a food allergen is the cow’s milk protein B-lactoglobulin (Bos d 5). This is a lipid binding protein with a beta barrel structure stabilized by two disulfide bonds, giving the protein its stability.”

5. A.
Api g 1. This homolog is also stable to thermal processing.

6. A.
Some alcoholic beverages contain residual levels of fining agents based on fish gelatin, milk casein, or egg albumin. These fining agents and their residues are highly modified compared with the raw foods. Individuals with diagnosis of allergies to fish and egg can have reactions to alcoholic beverages when they are used as fining agents. These reactions to fining agents in alcoholic beverages are rare.

7. A.
Proteins are removed during the refining process, and highly-refined oils contain very low levels of residual protein. Highly-refined soybean oils are considered safe for consumption by patients with soy allergies in Europe. Although, highly-refined peanut oils don’t appear to cause a reaction in peanut allergic individuals, these oils DO NOT have an EU labeling derogation.

8. B.
“Maillard modification of allergens can add to allergenicity with roasting and frying. Prolamin superfamily 2s albumin allergens retain their native structure after roasting and frying. Some cupin allergens (7S and 11S seed storage proteins) become insoluble with roasting. The peanut 2S albumin allergens retain their allergenic activity after roasting, which also explains why roasted peanuts possess significant allergenicity.”

9. D.
“Conformational epitopes are formed from various segments of a polypeptide chain that are brought together by protein folding. Many food processing procedures affect the way in which proteins are folded and can either destroy conformational epitopes found in proteins in unprocessed or raw foods or reveal new epitopes previously hidden by protein folding. Linear epitopes, which comprise short regions of about 8 to 15 amino acid residues and tend to be mobile, adopt a disordered secondary structure. They are likely to be stable in response to food processing procedures.”

10. A.
Allergy to deamidated gluten was described as a separate entity from wheat allergy by Denery-Papini et al. Deamidated gluten can thus cause severe allergic reactions in individuals who can otherwise consume wheat-containing foods. This was demonstrated by strong IgE binding to deamidated gliadins or peptides of the type QPEEPFPE.

(Denery-Papini S, Bodinier M, Larré C, et al.: Allergy to deamidated gluten in patients tolerant to wheat: specific epitopes linked to deamidation. Allergy (2012); 1023-32)
FIT Board Review Corner – February 2017

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Chapter 34 (pages 540-565): Atopic Dermatitis

1. What is the lifetime prevalence of atopic dermatitis in U.S. schoolchildren?
   a. 5%
   b. 13%
   c. 17%
   d. 25%

2. Which gene mutation has been associated with early-onset, severe and persistent atopic dermatitis?
   a. FLG
   b. SPINK5
   c. DOCK8
   d. FOXP3

3. The highest incidence of asthma at a given age has been observed in children with onset of AD before:
   a. 3 months
   b. 5 months
   c. 1 year
   d. 3 years

4. Which of the following is a true statement regarding filaggrin?
   a. FLG gene mutations have only been described in European Caucasian populations.
   b. Loss-of-function mutations in FLG are strongly associated with a risk of asthma when occurring with atopic dermatitis.
   c. Abnormal FLG expression in bronchial epithelium leads to increased risk of asthma.
   d. FLG is an enzyme that regulates the breakdown of the epidermal barrier.
5. Which pathogen is most often associated with AD?
   a. S.pneumo
   b. M.sympodialis
   c. S.aureus
   d. S.epidermidis

6. Which immunoregulatory abnormality is present in AD?
   a. Decreased synthesis of IgE.
   b. Decreased levels of specific IgE to multiple allergens (food, aeroallergens, microorganisms and enterotoxins).
   c. Increased expression of CD23 on B cells and monocytes.
   d. Decreased surface expression of FceR1 on antigen-presenting cells in the skin.

7. Which cytokines are upregulated in AD?
   a. IL-2, IL-5 and IL-6
   b. IL-4, IL-5 and IL-13
   c. IL-4, IL-5 and IL-13
   d. IL-5, IL-12 and IL-13

8. Which cytokines are secreted less by Th1 cells in AD?
   a. IFN-gamma
   b. TNF-alpha
   c. IL-4
   d. IL-13

9. Which lymphocytes are predominately seen in acute and chronic AD lesions via immunohistochemical staining?
   a. CD3, CD4, CD56
   b. CD4, CD8, CD45RO
   c. CD3, CD4, CD45RO
   d. CD3, CD45RO, CD45RA

10. What immunopathologic abnormality is seen in AD?
    a. Activated eosinophils are present in significantly great numbers in acute lesions than in chronic lesions.
    b. Keratinocyte apoptosis causes acantholysis and spongiosis.
    c. Vascular endothelial cells express abnormally low levels of E-selectin.
    d. Increased mast cells that have degranulated.
Answers

1. C.
2. A.
3. A.
4. B.
5. C.
6. C.
7. B.
8. A.
9. C.
10. B.
FIT Board Review Corner – March 2017

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Chapter 34 (pages 549-558): Atopic Dermatitis
Prepared by: Evelyn Lomasney, MD

1. Staphylococcal exotoxins induce CLA expression by stimulating skin dendritic cells to produce this cytokine.
   a. IL-12
   b. IL-5
   c. IL-31
   d. IL-4

2. Decreased levels of this protein have been associated with reduced water-binding capacity and increased transepidermal water losses in atopic dermatitis patients.
   a. Cholesterol
   b. Linoleic acid
   c. Palmitic fatty acid
   d. Ceramide

3. An 18-month-old girl is brought to your clinic by her mother with persistent atopic dermatitis lesions on bilateral arms and legs despite daily emollients and topical application of Desonide 0.05% cream. Mother reports they have been diligent in avoidance of irritants and skin care regimen. On exam there is no evidence of bacterial infection. What is the next best step in management?
   a. Switch to Mometasone 0.1% ointment daily
   b. Switch to Desonide 0.05% ointment daily
   c. Switch to Hydrocortisone 2.5% ointment daily
   d. Switch to Triamcinolone 0.1% daily

4. In Th2 driven skin disease such as atopic dermatitis, increased IL-4 and IL-13 can contribute to increased risk of infection through which mechanism?
   a. FLG Secretion of chemokines CCL5, CCL12 and CCL22
b. Suppression of defensins/cathelicidins
c. Synthesis of pro-IL 1β and pro-IL 18
d. Induced expression of defensins/cathelicidins

5. Topical calcineurin inhibitors pimecrolimus and tacrolimus are often utilized in the treatment of atopic dermatitis. By inhibiting the calcium-calmodulin dependent phosphatase calcineurin, these medications ultimately prevent the translocation of which transcription factor?
   a. AP-1
   b. NF-kB
   c. NFAT
   d. IκB

6. Which cytokine along with IL-5, this cytokine contributes to increased survival and infiltration of eosinophils in AD?
   a. IL-10
   b. GM-CSF
   c. CLA
   d. TSLP

7. In skin homing, 1,25(OH)₂D₃ and IL-12 increase expression of which E-selection ligand on lymphocytes?
   a. TARC
   b. CCL 17
   c. CLA
   d. CCL 1

8. A 4-year-old boy with history atopic dermatitis presents to your clinic with this rash. What is the management?
a. Oral Acyclovir  
b. Augmentin  
c. IV Acylovir  
d. Bactrim

9. Which A 34-year-old female with lifelong history of atopic dermatitis on arms, legs and face treated with as needed triamcinolone 0.1% cream presents to your clinic complaining of burning sensation on face. Examination shows erythema, scaling and follicular papules and pustules around mouth and scaling in alar creases. What is the management?  
a. Topical pimecrolimus  
b. Bactrim  
c. Discontinuation of all topical corticosteroids  
d. Prednisone burst

10. CCR4 binds with which chemokine in skin homing:  
a. CCL27  
b. CCL 16  
c. CCL1  
d. CCL17
Answers

1. A, page 549.
Toxins acting as super antigens can induce CLA expression by stimulating IL-12 production in dendritic cells. By stimulating epidermal Langerhans Cells and macrophages to secrete IL-1 and TNF-α, staphylococcal exotoxins can induce vascular endothelial E-selectin expression, which in turn could facilitate migration of CLA+ T cells to the area. Toxin-stimulated Langerhans Cells migrating to regional skin-associated lymph nodes act as antigen-presenting cells and could produce IL-12 locally, thereby increasing skin-homing capability of antigen stimulated T cells.

2. D, page 552.
The enzyme SM deacylase is highly expressed in the epidermis of AD patients and competes with sphingomyelinase or β-Glucocerebrocidase for the common substrate SM or glucosylceramide. This results in a ceramide deficiency of the stratum corneum. Decreased ceramide levels result in reduced water binding capacity, increase transepidermal water loss and decreased water content in the skin. Equimolar ratio of ceramide, cholesterol and lineolic acid (essential fatty acid) or palmitic or stearic acid (nonessential fatty acid) allows normal repair of damage skin. Alteration of these ratios affects skin barrier repair in Atopic Dermatitis.

3. D, pages 554-555
Management of persistent lesions despite avoidance of irritants an appropriate use of emollients and low potency topical corticosteroids requires escalation of steroid potency. Topical steroids are available in a variety of formulations ranging from Group 1 (high potency) to Group 7 (low potency). The vehicle in which the product is formulated ie ointment vs cream can alter potency strength. Also it is important to know the age appropriate indications when treating pediatric patients: fluticasone 0.05% cream, up to 28 days of in children age > 3months; fluticasone lotion in children age > 12 months; mometasone ointment in children > 24 months. See the chart below for different strengths of common topical steroids.

<table>
<thead>
<tr>
<th>Group</th>
<th>Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clobetasol propionate (Temovate) 0.05% ointment/cream</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate (Dipoten) 0.05% ointment/cream</td>
</tr>
<tr>
<td>2</td>
<td>Mometasone furoate (Elocon) 0.1% ointment</td>
</tr>
<tr>
<td></td>
<td>Halcinonide (Haloph) 0.1% cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinonide (Lidex) 0.05% ointment/cream</td>
</tr>
<tr>
<td></td>
<td>Desoximethasone (Topicort) 0.25% ointment/cream</td>
</tr>
<tr>
<td>3</td>
<td>Fluticasone propionate (Cutivate) 0.005% ointment</td>
</tr>
<tr>
<td></td>
<td>Halcinonide (Haloph) 0.1% cream</td>
</tr>
<tr>
<td></td>
<td>Betamethasone valerate (Velsone) 0.1% ointment</td>
</tr>
<tr>
<td>4</td>
<td>Mometasone furoate (Elocon) 0.1% cream</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetone (Kenalog) 0.1% ointment/cream</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetone (Synalar) 0.025% ointment</td>
</tr>
<tr>
<td>5</td>
<td>Fluocinolone acetone (Synalar) 0.025% cream</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone valerate (Westcor) 0.2% ointment</td>
</tr>
<tr>
<td>6</td>
<td>Desonide (DesOven) 0.05% ointment/cream/lotion/gel</td>
</tr>
<tr>
<td></td>
<td>Alclometasone dipropionate (Actovate) 0.05% ointment/cream</td>
</tr>
<tr>
<td>7</td>
<td>Hydrocortisone (Hytope) 2.5% and 1% ointment/cream</td>
</tr>
</tbody>
</table>
95% of dermal and epidermal T cells have a memory phenotype. CD4+ cells of each major subset, Th1, TH2, TH17 and Treg are found in the skin. Th1 and TH17 cells are important for microbial defense against intracellular and extracellular microbes. The TH17 cytokines, IL17 and IL-22 increase keratinocyte expression of the antimicrobial defensins and cathelicidins. In contrast, Th2 cytokines IL-4 and IL-13 suppress keratinocyte production of defensins and cathelicidins. This is thought to play a role in the increase susceptibility to infections seen in Th2 mediated skin disease ie atopic dermatitis.

The calcium-calmodulin dependent phosphatase calcineurin dephosphorylates inactive cytoplasmic NFAT, which uncovers a nuclear localization signal that allows active NFAT to translocate to the nucleus. NFAT binds the regulatory regions of IL2, IL4 and other cytokines, usually in association with AP-1, another transcription factor.

Conditions favoring persistent Th2 type response may be established in atopic dermatitis. In chronic atopic dermatitis, monocytes have lower incidence of spontaneous apoptosis due to increased production of GM-CSF. Along with IL-5, GM-CSF also contributes to the proliferation and survival of eosinophils.

7. C, page 550
In skin draining regional lymph nodes, 1,25(OH)2D3 and IL-12 induce expression of the E-selectin ligand cutaneous lymphocyte antigen (CLA) on effector T cells. Along with other home signals (CCR4, CCR8, CCR10) CLA directs migration of effector T cells to the skin.

8. C, page 555
This patient has disseminated eczema herpeticum also called Kaposi varicelliform eruption. Initial management usually requires systemic acyclovir. Recurrent cutaneous herpetic infections can be controlled with daily prophylactic oral acyclovir.

9. C, page 553
This patient presents with perioral dermatitis from medium potency corticosteroid use on her face. The burning sensation she feels is due to “steroid addiction” and often seen in middle age women from prolonged topical steroid use on the face. Treatment is discontinuation of all topical steroids.

10. D, page 550
In skin draining regional lymph nodes 1,25(OH)2D3 and IL-12 induce expression on CLA, CCR4, CCR8, CCR10 on effector T cells which direct migration of these T cells to the skin. The ligands for these chemokines are:
CLA-E Selectin/CD62E
CCL17/TARC – CCR4
CCL1 - CCR 8
CCL 27 – CCR 10
FIT Board Review Corner – April 2017

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Chapter 36 (pages 579-583): Urticaria and angioedema
Prepared by: Tammy Peng, MD

1. Which of the following characteristics are more consistent with urticarial vasculitis?
   a. Lesions are pruritic and raised in appearance.
   b. Lesions are painful, last longer than 48 hours and may leave purpura or ecchymosis.
   c. Lesions may be erythematous with central pallor.
   d. Lesions are more common in areas in which there is compression or friction of the skin.

2. Which condition is characterized by fever, urticarial and monoclonal gammopathy?
   a. Mastocytosis
   b. Cryoglobulinemia
   c. Muckle-Wells syndrome
   d. Schnitzler syndrome

3. Which of the following represents the most effective, first-line treatment for chronic urticaria?
   a. Second-generation H1 antihistamine (cetirizine, fexofenadine, loratadine)
   b. Corticosteroids
   c. H2 blocker
   d. First-generation H1 antihistamine (diphenhydramine, hydroxyzine)

4. Which of the following characteristics is typical of polymorphic eruption of pregnancy (PEP), also called pruritic urticarial papules and plaques of pregnancy (PUPPP)?
   a. Rash involves the face, palms and soles.
   b. Urticarial lesions that occur around the umbilicus.
   c. Lesions are triggered by pressure applied to the skin.
   d. Rash begins as papules within abdominal striae and spreads to involve the extremity.
5. Which of the following histamine-release associated features is seen in a chronic idiopathic urticarial (CIU) responder?
   a. ≤10% of cellular histamine content is released to optimal dose of cross-linking anti-IgE
   b. Syk same as or below normal
   c. Reduced SH2 domain-containing inositol 5-phosphatase (SHIP)-1 levels
   d. Tenfold higher dose response to anti-IgE in active disease
   e. Increased SH2 domain-containing inositol 5-phosphatase (SHIP)-2 levels

6. Skin biopsy of a lesion demonstrating a predominance of neutrophils consistent with neutrophilic urticaria would be seen in which disease?
   a. Hereditary autoinflammatory fever syndromes
   b. Chronic idiopathic urticaria
   c. Aquagenic Urticaria
   d. Dermatographism

7. Which of the following is the most common cause of chronic urticaria?
   a. Food allergies
   b. Physical urticaria
   c. Idiopathic urticaria
   d. Malignancy

8. Which of the following medications that can be used as an alternative therapy in antihistamine refractory chronic urticarial is preferred in urticarial vasculitis, delayed pressure urticarial and angioedema?
   a. Sulfasalazine
   b. Dapsone
   c. Omalizumab
   d. Calcineurin inhibitors (cyclosporine, tacrolimus)

9. Which of the following systemic diseases associated with urticarial lesions involves a mutation in cryopyrin?
   a. Mastocytosis
   b. Cryoglobulinemia
   c. Familial cold autoinflammatory syndrome
   d. Muckle-Wells syndrome
10. A 42-year-old woman presents to clinic with a two-month history of recurrent, pruritic rash. She reports that the rash usually develops in the evening often under the waistband of her pants. She also notes that she often has this same itchy rash on her shoulder after carrying her purse around for a few hours. What type of physical urticaria is most consistent with this patient’s history?
   a. Cholinergic urticaria
   b. Pressure-related urticaria
   c. Solar urticaria
   d. Vibratory urticaria
Answers

1. B, pages 579 & 582.
Skin lesions that are painful, that last more than 48 hours and that leave residual skin changes including ecchymosis are more suspicious for urticarial vasculitis. Eliciting a history with the presence of such lesions should prompt consideration for skin biopsy.

2. D, page 582.
Schnitzler syndrome is a rare systemic disorder in patients with monoclonal IgM or IgG (monoclonal gammapathy). Patients have associated symptoms of fever, weight loss, bone pain, adenopathy and urticaria thought to be secondary circulating immune complexes and complement activation.

3. A, page 582.
The most effective, first-line therapy for chronic urticarial is the use of new-generation antihistamines which include fexofenadine, loratadine and cetirizine. These medications are non-sedating, alleviate pruritus and reduce occurrence of wheals. Other options if these agents are only partial effective, one can consider 1) increasing the dose of the non-sedating antihistamine 2) addition of a sedating, older-generation antihistamine (diphenhydramine, hydroxyzine) 3) addition of H2 blocker 4) trial of a leukotriene pathway inhibitor.

Polymorphic eruption of pregnancy (PEP), also called pruritic urticarial papules and plaques of pregnancy (PUPPP) is a pruritic dermatitis that affects pregnant women. Typically, dermatitis begins as erythematous papules within abdominal striae with periumbilical sparing that then spread to the extremities and coalesce into urticarial plaques. Lesions can be target-like and usually spare the face, palms and soles. Of note, because of limited safety data, only loratadine and cetirizine are currently recommended for use in pregnancy.

Blood basophil IgE receptor responses in patients with chronic idiopathic urticarial (CIU) have been divided into two basophil phenotypes—CIU responders and CIU nonresponders. CIU nonresponder basophils do not degranulate to ex vivo IgE receptor activation and have elevated levels of IgE receptor regulating inhibitor phosphatases, SHIP-1 and SHIP-2. These two phenotypes are independent of autoimmune serum factor and reflect some differences in clinical features. While underlying disease mechanisms are still unclear, available evidence supports basophil responsiveness relevance to urticarial pathogenesis.

Histopathologic examination of an urticarial lesion will show perivascular leukocyte infiltrate composed of lymphocytes, eosinophils, neutrophils, and basophils as well as mast cells that have degranulated in the dermis. Neutrophilic predominance on skin lesion biopsy should prompt for evaluation of associated systemic diseases including adult-onset Still disease, Schnitzler syndrome, systemic lupus erythematosus and the hereditary autoinflammatory fever syndromes.
In 80% of cases of chronic urticaria where no external allergic cause or other disease process can be identified, the condition is called chronic idiopathic urticarial. Approximately 20% of patients with chronic urticaria have a reproducible physical trigger for their skin lesions (called physical urticarial).

8. B, page 582.
There is limited evidence on use of dapsone in chronic urticaria, especially in neutrophilic urticarial. Dapsone is preferred in treatment of urticarial vasculitis, delayed pressure urticarial and angioedema. Patients on dapsone should be monitored for anemia, neuropathy and methemoglobinemia. Other treatments of chronic urticaria that serve as alternative to corticosteroids in antihistamine resistant cases include sulfasalazine, hydroxychloroquine, calcineurin inhibitors, mycophenolate and omalizumab.

Muckle-Wells syndrome is associated with mutations in cryopyrin. Patients often have sensorineural hearing loss and are similar to patients with familial cold autoinflammatory syndrome, with the exception that patients are not cold-sensitive. Patients with familial cold autoinflammatory syndrome often present in infancy with symptoms including periodic fever, urticaria, leukocytosis, conjunctivitis and muscle and skin tenderness after exposure to cold.

There are two described forms of pressure-related physical urticarial/angioedema. In the first form, urticarial develops shortly after pressure is applied to the skin, similarly to dermatographism. A second delayed-onset form appears several hours after at the site of pressure (in our patient’s example, under the waistband of her pants or under the strap of her purse). Skin biopsies from patients with delayed-onset urticarial demonstrate both neutrophils and eosinophils.
FIT Board Review Corner – May 2017

Welcome to the FIT Board Review Corner, prepared by Tammy Peng, MD, and Amar Dixit, 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 37 (pages 588-599): Hereditary Angioedema and Bradykinin-Mediated Angioedema (top) Prepared by: Sarah Spriet, DO

1. Patient is a 45-year-old female who reports recurrent episodes of asymmetric, nondependent swelling. Each episode is gradual in onset and there is no associated urticaria, respiratory, gastrointestinal or cardiovascular symptoms. Screening labs reveal a low C4, low C1 INH function and a normal C1q level. What is the pathophysiology of her condition?
   a. Mutation in the SERPING1 gene.
   b. Unknown.
   c. Excessive consumption of C1 inhibitor.
   d. Inhibition of bradykinin catabolism.

2. Which of the following is the most common form of bradykinin-mediated angioedema syndromes?
   a. Type I HAE
   b. Type II HAE
   c. HAE with normal C1 INH
   d. Acquired C1 INH deficiency

3. Which of following statements regarding hereditary angioedema with normal C1INH is true?
   a. This condition affects 50% of male and female children of parents with HAE equally.
   b. This condition is more likely to manifest before puberty.
   c. Patients tend to have more attacks with fewer attack-free intervals compared to HAE type I/II.
   d. A higher percentage of swelling episodes affects the face and tongue.

4. Appropriate laboratory testing for bradykinin-mediated angioedema includes measurement of which of the following?
   a. Complement C3
   b. Complement C4
c. C1q binding antigen
d. Factor XII

5. For the highest sensitivity, C1INH function should be measured by what type of assay?
   a. Chromogenic
   b. ELISA
   c. Immunofluorescence
   d. Nephelometry

6. Which of the following drugs antagonizes the bradykinin receptor?
   a. anakinra
   b. ecallantide
   c. icatibant
   d. recombinant C1INH

7. Which of the following is an on-demand treatment for HAE attacks?
   a. danazol
   b. ecallantide
   c. fresh frozen plasma
   d. Tranexamic acid

8. Which of the following statements is true?
   a. Use of an indwelling catheter or port for prophylactic C1INH administration is encouraged due to frequent infusions.
   b. The optimal dose for the prophylactic medications should be based on the patient’s C1INH and C4 levels.
   c. Birth control pills and estrogen replacement therapy are considered adjunctive treatments in the management of HAE.
   d. Plasma derived C1INH concentrates are approved for use in children as young as 6 years and have been effective in younger children.

9. Which of the following agents is preferred for long-term HAE prophylaxis during pregnancy?
   a. danazol
   b. icatibant
   c. plasma-derived C1INH
   d. tranexamic acid
10. A patient on long-term HAE prophylaxis is complaining of new onset vertigo and muscle cramps. Which of the following drugs is responsible for these side effects?
   a. icatibant
   b. plasma-derived C1INH
   c. stanozolol
   d. tranexamic acid
Answers

The question stem describes a patient with HAE. In HAE types I and II, the C4 and C1 INH function are reduced and the C1q level is normal (see Table 37-1). The fundamental abnormality in both type I and type II HAE is a mutation of the C1 INH gene (SERPING1). If the C1q level were also low, this patient would have acquired C1 INH deficiency due to excessive consumption of C1 inhibitor. These screening labs would all be normal if the patient had HAE with normal C1 INH or ACE-I associated angioedema. The pathophysiology of HAE with normal C1 INH is unknown. ACE cleaves bradykinin and substance P into inactive peptides. Therefore, the inhibition of ACE results in a reduction in bradykinin metabolism.

The overall prevalence of HAE due to C1 INH deficiency is not well defined, but is estimated to range from 1:30,000 to 1:80,000 in the general population. Type I is the most common form of HAE due to C1 INH deficiency, accounting for 85% of the cases, with type II accounting for the other 15%. Because of the lack of clear diagnostic criteria for HAE with normal C1 INH level, no estimates can be made regarding its overall prevalence or distribution. Acquired C1 INH deficiency is a sporadic disease. It is relatively rare, with an estimated prevalence between 1:100,000 and 1:500,000, although many cases may not be recognized or diagnosed.

The clinical presentation of HAE with normal C1 INH superficially resembles that of HAE associated with reduced C1 INH function; however, a number of subtle but important differences have been observed. HAE with normal C1 INH is differentiated from that associated with reduced C1INH function as follows: It is more likely to affect females; it is less likely to manifest before puberty; patients tend to have fewer attacks, with more attack-free intervals; and the distribution of attacks includes a higher percentage of facial and tongue episodes, a lower percentage of abdominal episodes and fewer multiorgan attacks.

C1INH deficiency should be investigated in patients with recurrent angioedema without urticaria who are not taking an ACE inhibitor. A diagnosis of C1INH deficiency requires laboratory confirmation with measurement of the complement C4 level, C1INH antigen level, and C1INH functional level. The C4 level is an excellent screening tool for C1INH deficiency in patients older than 1 year of age, with a reduced C4 level even between attacks in at least 95% of patients with C1INH deficiency, increasing to virtually 00% during angioedema attacks. Serum C3 level may also be reduced, but is not the best answer choice as it may be reduced or increased in a variety of conditions. C1q binding antigen assay detects circulating immune complexes and is not helpful in the evaluation of bradykinin-mediated angioedema. In a subset of patients with HAE with normal C1INH, the disorder is associated with a mutation in coagulation factor XII; however, the mutation itself has not yet been unequivocally demonstrated to cause the disease. Evaluating for Factor XII mutation is not part of the screening or initial workup for suspected bradykinin-mediated angioedema.

The chromogenic assay is recommended based on the high sensitivity, clear distinction and low variability. It measures the inhibition of C1s activity by C1 inhibitor. ELISA assay detects the complexes formed between C1INH and C1r or C1s following activation of C1. See also: Wagenaar-Bos IG, et al. Functional C1 inhibitor diagnostics in HAE: assay evaluation and recommendations. J Immunol Methods. 2008;338:14-20.

Icatibant antagonizes bradykinin effects at the bradykinin B2 receptor. Anakinra is a recombinant IL1 receptor antagonist used to reduce the pain and swelling associated with rheumatoid arthritis. Anakinra is not indicated in the treatment of HAE with C1INH deficiency. Ecallantide is a recombinant protein which inhibits the conversion of high molecular weight kininogen to bradykinin by selectively and reversibly inhibiting plasma kallikrein. Recombinant C1NH inhibits plasma kallikrein, coagulation factors XIIa, XIIIf and Xia, C1s, Cr, MASP-1, MASP-2 and plasmin.

Four drugs – plasma derived C1INH, ecallantide, icatibant and recombinant human C1INH – have been shown to be safe and effective for the acute treatment of HAE attacks. Plasma contains C1INH and is effective in abrogating HAE attacks. Plasma may, however, occasionally induce an acute exacerbation of the attack, presumably because plasma contains high molecular weight kininogen in addition to C1INH. For this reason, caution is required with use of plasma to treat an HAE attack. Because of the potential concern regarding the viral safety of fresh frozen plasma, solvent detergent-treated plasma is preferred. Because newer effective therapies have become available, the only indication for the use of fresh frozen plasma for acute HAE attacks will be if the more effective specific therapy is not available. Therefore, ecallantide is the best choice. Attenuated androgens (i.e. danazol) and antifibrinolytic agents (i.e. tranexamic acid) are not effective for acute angioedema attacks.

The use of an indwelling catheter or port is discouraged for bi-weekly plasma-derived C1INH replacement infusions due to the increased risks of infection or thrombosis. The optimal dose for the prophylactic medications should be based on the clinical response, rather than on any lab results. Oral contraceptive pills and estrogen replacement therapy both often increase the frequency of swelling and should be avoided in all women with HAE.

Pregnancy can be associated with an increase in the frequency and severity of HAE episodes. Treatment with androgens is contraindicated during pregnancy, and plasma-derived C1INH is preferred if long-term prophylaxis is required. Icatibant is an on-demand medication. Tranexamic acid is an antifibrinolytic agent that may provide somewhat effective and relatively safe long-term HAE prophylaxis but generally is less effective than androgen regimens.

10. D, pages 598-599.
Common side effects of the antifibrinolytic drugs include nausea and diarrhea, vertigo, postural hypotension, fatigue, and muscle cramps or weakness with an increase in muscle enzyme concentrations. There is also a theoretical risk of thrombosis with these drugs. Icatibant is an on-demand HAE drug that is commonly associated with discomfort at the injection site. Plasma-derived C1INH is a normal protein found in the plasma of all people. Chronic use of plasma-derived C1INH is
associated with the burden of IV administration, as well as potential for complications such as anaphylaxis, thrombosis or infection. The most common side effects from the 17α-alkylated androgens include virilization in women along with menstrual irregularities, acne, changes in libido, changes in mood, increased aggression, alterations in the lipid profile, weight gain and hypertension. Because these drugs can cause hepatotoxicity, including development of hepatic adenomas and hepatic carcinoma, periodic liver enzyme monitoring and ultrasound imaging are recommended.
FIT Board Review Corner – June 2017

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Review Questions

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Chapter 38 (pages 603-615): Immune Complex-Mediated Diseases
Prepared by: Kara Wada, MD

1. Immune complexes tend to be largest under which of the following conditions?
   a. Extreme antigen excess
   b. Extreme antibody excess
   c. Extreme antibody excess
   d. Inhibition of bradykinin catabolism.

2. Which of the following is the most common form of bradykinin-mediated angioedema syndromes?
   a. Type I HAE
   b. CR2
   c. FcγRI
   d. FcγRII

3. These specialized cells aid in the development of germinal centers by binding but not endocytosing immune complexes for weeks to months at a time.
   a. CD4+ T cells
   b. Follicular helper cells
   c. Plasmacytoid dendritic cells
   d. Follicular dendritic cells
4. What has been shown to be the earliest event in an active Arthus reaction?
   a. Margination of the polymorphonuclear cells
   b. Immune complex and complement deposition
   c. Intravascular platelet clumping
   d. Red blood cell extravasation

5. Which pathophysiologic condition is more characteristic of acute serum sickness as opposed to chronic serum sickness as demonstrated in the rabbit model?
   a. Arteritis
   b. Nephritis
   c. Arthritis
   d. Urticarial rash

6. How long after drug initiation does serum sickness typically develop in a patient with no prior exposure to the medication in question?
   a. 24-48 hours
   b. 3-5 days
   c. 1-3 weeks
   d. 1-2 months

7. Which medications are most commonly implicated in drug-induced serum sickness?
   a. Penicillins, sulfonamides, beta blockers
   b. Sulfonamides, hydantoins, ACE-inhibitors
   c. Thiazides, penicillins, antihistamines
   d. Tranexamic acid

8. Which of the following statements is true?
   a. Use of an indwelling catheter or port for prophylactic C1INH administration is encouraged due to frequent infusions.
   b. Low levels of circulating immune complexes correlates with high clinical disease activity.
   c. Circulating immune complexes and FcγR-specific clearance defects are believed to be important in SLE pathogenesis.
   d. They have increased numbers of CR1 receptors on their erythrocytes.

9. Which glomerular disease is associated with anti-glomerular basement membrane zone antibodies?
   a. Goodpasture syndrome
b. Poststreptococcal glomerulonephritis

c. Lupus nephritis

d. Membranoproliferative glomerulonephritis

10. Which therapy for autoimmune diseases and its mechanism are correctly paired?

a. Rituximab depletes plasma cells

b. Proteosome inhibitors (bortezomib) destroy CD20 cells.

c. Plasmapheresis removes antibodies and/or immune complexes.

d. IVIG causes a downregulation through FcyRI receptors.
Answers

At equivalence, immune complexes tend to be large because the chances for cross-linking are optimized.

Large immune complexes efficiently activate complement by rapidly binding to the CR1 (CD35/C3b receptor) on the surface of RBCs which then transport them to the liver for Kupffer cells to remove and phagocytose them.

Follicular dendritic cells (FDCs) are associated with germinal cell development. FDCs bind but do not endocytose immune complexes and are able to harbor complexes on their surface for weeks to months at a time. Immune complex-bound FDCs are crucial for the growth and maintenance of high-affinity B cells in the germinal center and the subsequent production of high-affinity antibody.

Immunofluorescent studies show that the earliest event in active Arthus reactions is the deposition of antigen-antibody complexes and complement in and around blood vessel walls.

5. A, page 609.
In the rabbit model of chronic serum sickness, animals did not develop arteritis which was characteristic of acute serum sickness.

Generally, serum sickness occurs 1 to 3 weeks after the start of administration of the medication. It can occur within 12-36 hours in patients who have been previously sensitized to the medication.

Fc-mediated reticuloendothelial system (RES) clearance has been shown to be defective. High levels of circulating immune complexes correlate with high clinical disease activity. Circulating immune complexes and FcγR-specific clearance defects are believed to be important in SLE pathogenesis. They have decreased numbers of CR1 receptors on their erythrocytes.

Goodpasture syndrome is associated with anti-glomerular basement membrane antibodies whereas the remaining 3 conditions are associated with immune complex deposits causing a “lumpy-bumpy” pattern on immunofluorescence.

Rituximab depletes CD20 B cells whereas proteasome inhibitors destroy plasma cells. IVIG causes a downregulation through FcγRIIB receptors.
FIT Board Review Corner – July 2017

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Chapter 39 (pages 616-633): Allergic and Immunologic Diseases of the Eye
Prepared by: Dr. Shahab Virani

1. A 30 year old male presents with itchy and watery eyes. He notes that he has been having this problem increasingly occur over the past several years. He reports that his symptoms are worst from May to August. He normally doesn’t do anything to treat his eyes but this year his symptoms are worse. He reports that he keeps his house clean, doesn’t own any pets and does not have any unique occupational exposures. He denies any visual disturbances, asthma, or eczema. Exam is notable for conjunctival hyperemia and Allergic Shiners. What is the most likely diagnosis?
   a. Seasonal allergic conjunctivitis (SAC)
   b. Perennial allergic conjunctivitis (PAC)
   c. Atopic keratoconjunctivitis (AKC)
   d. Giant papillary conjunctivitis (GPC)

2. The treatment of choice for mild to moderate allergic conjunctivitis
   a. Histamine H1 Receptor Antagonist
   b. Mast Cell Stabilizer
   c. Histamine H1 Receptor Antagonist + Mast Cell Stabilizer

3. The two most unique and accepted granule associated neutral proteases phenotypes include
   a. Tyrptase, Chymase
   b. Tryptase, histamine
   c. Lipase, Chymase
   d. Lipase, histamine
4. A 45 year old female comes to your clinic with itchiness of her eyes. She reports that she has chronic ocular pruritus, redness in her eyes, difficulty with light, and sometimes pain. When going through her history she reports that she always feels dry and has problems with dry skin. Her eyes feel like leather and you notice she has lost her eyelashes. She has problems with seasonal allergies, and asthma. She also endorses owning a large Alaska Husky. She also denies any vision problems requiring glasses or contacts. What is the diagnosis?
   a. Giant Papillary Conjunctivitis
   b. Peripheral Ulcerative Keratitis
   c. Vernal Keratoconjunctivitis
   d. Atopic Keratoconjunctivitis

5. Which of these medications is both Histamine H1 receptor Antagonist and Mast Cell stabilizer.
   a. Antazoline
   b. Azelastine
   c. Bepotastine
   d. Cromolyn

6. A nine year old boy is brought into your clinic because of redness in his eyes. His medical history was notable for seasonal allergic rhinitis, asthma, and eczema. He is originally from West Africa but recently moved to Italy. His main complaints include significant ocular pruritus, sensitivity to light and feeling like something is stuck in his eye. On exam his sclera are injected and his R eyelid is lower than his Left. You try to examine his conjunctiva and you see this

![Image Taken from Middleton](image)

What is the diagnosis?
   a. Giant Papillary Conjunctivitis
   b. Peripheral Ulcerative Keratitis
   c. Vernal Keratoconjunctivitis
   d. Atopic Keratoconjunctivitis
7. A 25 year old male presents for conjunctival provocation testing to Birch. You want to use a standardized approach so you chose the most widely accepted protocol from Abelson and coworkers. You perform the testing and figure out the threshold dose of allergen extract that elicits symptoms. How many days later should you have the patient back in order to establish reproducibility to the Birch extract?
   a. 3 Days
   b. 5 Days
   c. 7 Days
   d. 14 Days

8. A 45 year old woman with a history of rheumatoid arthritis has been noticing over the past several days that both of her eyes have been getting increasingly red. In addition she has also developed severe pain which she describes as “deep and boring”. Because the pain was so severe she tried some of her husband’s eye drops (10% phenylephrine). None of her symptoms got better and now her vision is getting slightly blurry. She denies any fever, chills, night sweats or eye discharge. Which of the following is the diagnosis?
   a. Episcleritis
   b. Allergic Conjunctivitis
   c. Foreign Body Trauma
   d. Scleritis

9. What would be the best treatment to the patient in Question 8 above?
   a. Topical steroids
   b. Acetaminophen PO
   c. Ibuprofen PO

10. In patients with Uveitis which location is generally the most affected.
    a. Anterior
    b. Intermediate
    c. Posterior
Answers

   The two forms of allergic conjunctivitis are defined by whether the inflammation and symptoms occur seasonally (spring, fall) or perennially (year-round). A majority of cases of seasonal allergic conjunctivitis and is related to pollens (e.g., grass, trees, ragweed) that appear during specific seasons. The distribution of SAC depends largely on the climate. The dominant symptom reported in allergic conjunctivitis is ocular itching.

   The mast cell–stabilizing component of these drugs benefits patients most if treatment is started before the height of symptom severity. Patients usually note rapid onset of relief of itch upon drop instillation, because most dual-action medications have high histamine H1 receptor affinity. Drug dosing will range from one to four times per day, and efficacy is judged best by symptom relief.

   Synthesis of inflammatory mediators varies according to the phenotype and tissue location of the mast cell. Granule-associated neutral proteases (tryptase and chymase) unique to mast cells generally are accepted as the most appropriate phenotypic markers to categorize human mast cells into subsets. On this basis, mast cells have been divided into MC_T (tryptase) and MC_TC (tryptase/chymase) phenotypes.

   Onset of disease occurs later in life from 2nd through 5th decade. Clinical features include itching, watery, mucus discharge, redness, blurring of vision, photophobia, and pain. Exacerbation occurs most frequently with fur bearing animals. The skin of the lids become leather like with development of cicatrical ectopion ectropion (turning outward of the lid from skin scarring) and lagophthalmos (incomplete closure of eyelids). Lateral canthal ulceration and cracking as well as lash loss (madarosis) also may be present. The lack of contact lens wear aids in differentiating AKC from GPC. Patients with AKC usually are older and exhibit major lid skin involvement compared with patients with VKC.

   Please refer to chart for drug and classification.
Vernal Keratoconjunctivitis occurs before age 10. Males predominate younger ages. It occurs when the patients are in hot and dry climates. Mediterranean and West African areas are the most affected populations. Atopic History is positive between 40-75% of patients. Sx include severe itching, photophobia, ptosis, thick mucus discharge, blephorospasm. The tarsal papillae that develop are usually greater than 1mm in diameter and have flattened tops.

A second baseline (7 days later) visit is necessary to establish reproducibility of the ocular allergic reaction threshold dose of the allergen extract.

Scleritis is differentiated from Episcleritis by symptom of severe pain (often described as deep and boring). Additionally, all redness of episcleral origin will blanch within 20 minutes of application of single drop of 10% phenylephrine. 40% of patients with Scleritis also have a systemic disease like RA.

Treatment of any form of Scleritis with steroid eye drops has been considered to be infective. Mainstay of treatment for all types of Scleritis has typically been oral nonsteroidal agents, oral steroids or oral immunosuppressive agents.

Anterior uveitis accounts for about 70%, intermediate 20% and posterior 5%-10%.
FIT Board Review Corner – August 2017

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Chapter 40 (pages 640-651): The Nose and Control of Nasal Airflow
Prepared by: Dr. Kristen Dazy

1. The growth of the nasal airway is formed from which primal embryonic germ layer?
   a. Ectoderm
   b. Mesoderm
   c. Endoderm
   d. Neural crest

2. Which gas is produced in high concentration by human paranasal sinuses and is responsible for antimicrobial and vasodilatory activity in the nasal airway?
   a. Oxygen
   b. Carbon dioxide
   c. Nitric oxide
   d. Helium

3. What type of epithelium can be found in the nasal vestibule and nasopharynx?
   a. Olfactory epithelium
   b. Simple squamous epithelium
   c. Stratified squamous epithelium
   d. Pseudostratified ciliated columnar epithelium

4. Which cranial nerve is responsible for nasal sensation of airflow?
   a. Olfactory nerve (CN I)
   b. Trigeminal nerve (CN V)
   c. Facial nerve (CN VII)
   d. Vestibulocochlear nerve (CN VIII)
5. Which of the following is the primary regulator of nasal airway resistance?
   a. Nasal vestibule
   b. Nasal valve
   c. Nasal septum
   d. Inferior turbinate

6. Nasal resistance is highest at which point in time?
   a. Age 0-12 months
   b. Age 3-12 years
   c. Age 13-25 years
   d. Age 26-75 years

7. The spontaneous and often reciprocal changes in unilateral nasal airflow, commonly referred to as the nasal cycle, is associated with which of the following?
   a. Parasympathetic nervous system
   b. Nasal chemosensors
   c. Airway humidification
   d. Nasal venous sinuses

8. Which of the following would be expected to decrease nasal resistance to airflow?
   a. Movement from an erect to supine position
   b. Movement to a lateral recumbent position
   c. Exercise
   d. Hyperventilation

9. Which histamine receptor(s) mediate the effects of histamine on the human nose?
   a. H1 receptor
   b. H2 receptor
   c. H3 receptor
   d. Both A & B

10. Which of the following treatments would be most effective in reducing nasal airway resistance associated with nasal challenge in grass pollen allergic patients?
    a. H1 antihistamine (oral)
    b. H1 antihistamine (topical)
    c. Intranasal corticosteroids
    d. Bradykinin antagonist
Answers

   The growth of the nasal airway is preceded by the formation of an olfactory placode from ectoderm in the 5-mm embryo.

   Nitric oxide (NO) is produced continuously by an inducible NO synthase expressed in healthy sinus epithelium. High levels of NO in the sinuses can defend against infection whereas reduced NO production can increase susceptibility to sinus infections. NO is inhaled with every breath and acts as an “aerocrine” hormone to enhance pulmonary oxygen uptake and reduce pulmonary vascular resistance.

   The nasal vestibule and nasopharynx is lined with a stratified squamous epithelium similar to that of the facial skin. Posterior to the nasal vestibule, the skin gradually changes into a ciliated respiratory epithelium. The typical respiratory epithelium is a pseudostratified ciliated columnar type that rests on a continuous basement membrane. Specialized olfactory epithelium with ciliated receptor cells is found in the olfactory area.

   Sensory innervation to the nose is supplied mainly by the olfactory and trigeminal nerves. Olfactory nerves enter the nose through the cribriform plate and form a distinct olfactory area. The majority of the sensory nerves to the nasal epithelium and nasal vestibule are supplied by two branches of the trigeminal nerve, the ophthalmic and maxillary nerves. The trigeminal nerves provide the sensations of touch, pain, hot, cold, and itch, as well as the sensation of nasal airflow which is perceived as a cool sensation upon inspiration.

5. B, page 645, Figure 40-3.
   Nasal airway resistance is regulated at the level of the nasal valve (also the narrowest point of the nasal passageway). The nasal valve is a dynamic structure and is controlled by swelling and construction of the venous sinuses of the inferior turbinate and nasal septum. Overall, nasal airway resistance has 4 components: the nasal vestibule, the bony entrance of the nasal cavum, the erectile tissue of the inferior turbinate, and the nasal septum.
6. A, page 646.
Nasal resistance is at a maximum during infancy. Many infants are described to be “obligatory nasal breathers” during the first few months of life, and therefore nasal obstruction in infancy can cause distress and may also disturb suckling and growth. In general, nasal resistance declines to the adult value by 16-18 years of age and then shows a slow decline with increasing age.

The term nasal cycle describes the spontaneous and often reciprocal changes in unilateral nasal airflow that are associated with congestion and decongestion of the nasal venous sinuses which are under the influence of the sympathetic nervous system. Nasal chemosensors and airway humidification are general functions of the nose, but do not directly influence the direction of nasal airflow (pages 644-645).

Exercise causes a generalized increase in sympathetic nervous activity with an increase in heart rate, bronchodilation and decreased nasal resistance to airflow. Answer choices A, B, and D all result in increased nasal airway resistance.

Histamine is a potent vasodilator which influences nasal airflow by causing congestion of the nasal venous sinuses. The effects of histamine are mediated by H1 and H2 receptors. Both are involved in the dilation of the venous sinuses, but only the H1 receptors are involved in sneezing, itching and hypersecretion. Thus, this may explain why H1 antihistamines are relatively ineffective in treating nasal congestion associated with nasal allergy and histamine challenge.

Unlike the H1 antihistamines which have a small effect on nasal congestion, intranasal corticosteroids are thought to provide relief of the symptom of nasal congestion associated with allergic rhinitis and has been shown to be effective in reducing the increased airway resistance that is associated with nasal challenge using grass pollen in allergic patients. Although bradykinin would also have an effect on nasal blood vessels and sensory nerves, no suitable antagonist has yet to be discovered.
FIT Board Review Corner – September 2017

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Chapter 41 (pages 652-663): Nasal Provocation Testing
Prepared by: Ashmi Doshi, MD

1. All of the following are clinical indications for nasal provocation testing, except:
   a. Differentiating sensitization and allergy
   b. Identifying the most relevant allergens in considering allergen immunotherapy
   c. Evaluating patients with extranasal symptoms upon exposure to allergens
   d. Initiating evaluation of allergy testing

2. What is the cut off for FEV1 prior to nasal provocation testing?
   a. $\geq 50\%$
   b. $\geq 60\%$
   c. $\geq 70\%$
   d. $\geq 80\%$

3. Which method of nasal fluid collection is optimal for measurement of biomarkers?
   a. Nasal blowing
   b. Cotton tip applicator method
   c. Nasal lavage
   d. Filter disk or strip

4. Which answer correctly describes the PNIF (peak nasal inspiratory flow) using a modified Youlten peak flow meter?
   a. It is independent of lung capacity
   b. It is best performed at the same time as allergen challenge
   c. It is best performed before and after allergen challenge
   d. Sensitivity and specificity do not compare with more expensive techniques
5. Which answer correctly describes acoustic rhinometry?
   a. It is most accurate for the anterior aspect (2-6cm) of the nasal passage
   b. It is most accurate for the posterior aspect (>6 cm) of the nasal passage
   c. It is performed on both nostrils at the same time
   d. It is not useful in measuring responses to nasal provocation

6. Which statement correctly identifies early phase response (EPR) and late phase response (LPR) to allergen challenge?
   a. EPR markers are primarily cytokines and markers of eosinophil activation, while LPR markers are typically those of mast cell and basophil degranulation and glandular secretion.
   b. EPR markers are primarily cytokines and glandular secretion, while LPR are those of mast cell and basophil degranulation and eosinophil activation.
   c. EPR markers are primarily mast cell and basophil degranulation and glandular secretion, while LPR markers are typically those of cytokines and markers of eosinophil activation.
   d. EPR markers are primarily mast cell and basophil degranulation and cytokines, while LPR are typically those of eosinophil activation and glandular secretion.

7. Which answer correctly identifies the phenomenon of “priming” in the nasal mucosa?
   a. Threshold doses required to provoke symptoms decrease during times of persistent allergen exposure.
   b. Threshold doses required to provoke symptoms increase during time of persistent allergen exposure.
   c. Annual allergen challenge results in decreased threshold dose to provoke symptoms.
   d. Annual allergen challenge results in increased threshold dose to provoke symptoms.

8. Which answer choice correctly identifies the biochemical substance with its mechanism of action?
   a. Histamine acts primarily on H2>H1 receptors
   b. Methacholine acts primarily on cholinergic receptors
   c. Adenosine monophosphate acts on adenosine A2b receptors
   d. PGE2 acts on CRTH2 receptors

9. Which of the following is true regarding physical triggers in nasal provocation testing?
   a. Neural mechanisms are responsible for increased susceptibility to physical triggers
   b. Histamine is the key mediator in nasal provocation by physical triggers
   c. Warmed air with humidity >60% is used to test physical triggers
   d. Hypertonic saline and mannitol do not induce mast cell degranulation
10. Which receptor is activated by capsaicin and may induce neuropeptide release from nerve endings?
   a. H2
   b. TRPV-1
   c. H3
   a. A2b
Answers

1. D, pg. 652, last paragraph of first section.
A-C are all clinical situations were nasal provocation testing may be useful.

2. B, pg. 653, first paragraph.
FEV1 should be checked in all patients prior to nasal provocation testing, and in those who have an
FEV1<60% predicted, it should not be done.

3. C, page 654, Table 41-1.
Nasal lavage allows for ample volume, and can measure biomarkers in fluid and cells.

It is best performed before and after allergen challenge.

5. A, page 654, Measures of Nasal Airway Patency, last paragraph.
Acoustic rhinometry is most accurate for the anterior aspect of the nose and is performed in each
nostril independently.

6. D, Pages 655-656, first paragraph under Biomarkers within Nasal Fluid, and table 41-2.
Biomarkers can be broadly divided into markers of EPR and LPR. EPR is typified by mast cell and
basophil degranulation, and glandular secretion and plasma exudation, and LPRs consist of cytokine
secretion and markers of eosinophil activation.

7. A, page 658, 1st paragraph under mucosal priming and repeat nasal challenges.
Persistent allergen exposure during the pollen season is accepted to have a priming effect on the
mucosa. Threshold doses required to provoke symptoms decrease during times of persistent
allergen exposure.

8. C, page 659, Table 41-3.
AMP acts on adenosine A2b receptors on primed airway mucosal mast cells, causing degranulation
and release of inflammatory mediators.

Neural mechanisms seem to be responsible for increased susceptibility in some individuals to
rhinorrhea and nasal congestion.

Capsaicin is an activator of TRPV-1 ion channels, located on sensory nerve endings.
**FIT Board Review Corner** – October 2017

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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 42a (pages 664-671): Allergic and Nonallergic Rhinitis
Prepared by: *Jackie Eastman, MD*

1. All of these are factors that influence the development of allergic rhinitis except:
   a. Female gender
   b. Particulate air pollution
   c. Grass pollen counts
   d. Maternal smoking

2. Medications associated with rhinitis include all of the following except:
   a. Estrogen
   b. Sildenafil
   c. Ibuprofen
   d. Beta blockers

3. Bacteria associated with primary atrophic rhinitis include:
   a. Staphylococcus aureus
   b. Streptococcus pneumoniae
   c. Klebsiella ozaenae
   d. Staphylococcus epidermidis

4. A child with chronic unilateral nasal obstruction and purulent secretions should be suspected of having:
   a. Allergic rhinitis
   b. Adenoid hypertrophy
   c. Atrophic rhinitis
   d. Foreign body in the nose
5. A defining symptom of empty nose syndrome, due to excessive resection of the inferior and, possibly, middle turbinates during surgery is:
   a. Dyspnea
   b. Halitosis
   c. Purulent discharge
   d. Nasal crusting

6. Categories of work-related rhinitis include all of the following except:
   a. Irritant
   b. Cytotoxic
   c. Corrosive
   d. Immunologic

7. Frequent viral respiratory infections in early childhood may protect against allergic rhinitis due to the following immunologic change:
   a. Non-allergic T helper cell phenotype
   b. Eosinophilic phenotype
   c. Cytotoxic T-lymphocyte phenotype
   d. Neutrophilic phenotype

8. What is true about the relationship between chronic rhinitis and asthma?
   a. All patients with asthma have chronic rhinitis
   b. Asthma exacerbations lead to sinusitis exacerbations
   c. Some patients with nasal allergy have nonspecific bronchial hyperresponsiveness without overt asthma symptoms
   d. Asthma leads to the development of chronic rhinitis.

9. Rhinitis symptoms are worse in the morning for most patients, irrespective of cause, because:
   a. All patients are allergic to/irritated by dust mites
   b. Most patients drink coffee which causes nasal congestion
   c. A supine position causes worsening nasal congestion
   d. Circadian variations of inflammation lead to highest levels of inflammation in the morning

10. The preferred way to image the sinuses include:
    a. X-ray
    b. CT with contrast
    c. CT without contrast
    d. MRI
Answers

1. C, pg. 665, a significant inverse association has been found between grass pollen counts and lifetime prevalence of symptoms of allergic rhinitis (meaning the more pollen the less likely you are to have allergic rhinitis). This is thought to be from the effects of rural living and presence of endotoxins in the environment, not the direct effect of pollen.

2. A, pg. 670, although changes in hormone levels have been attributed to rhinitis in pregnancy, this has not been shown in patients taking exogenous ovarian hormones. The rest have anecdotally been associated with rhinitis.

3. C, pg. 670, primary atrophic rhinitis is prevalent in areas with prolonged warm seasons and typically afflicts middle-aged adults. Many patients have chronic bacterial infections due to a large number of organisms, including Klebsiella ozaenae. Staphylococcus aureus is associated with chronic rhinosinusitis.

4. D, pg. 671, a small object, such as a button or piece of a small toy, can fall into a posterior position and is not always visible. This is typically a young child who will adamantly deny putting anything up their nose. The other options typically have bilateral symptoms.

5. A, pg. 670, patients with this syndrome cannot sense airflow through the nose, even though it is completely open. This can lead to a profound sense of dyspnea in the absence of any objective findings of pulmonary disease. The rest are common symptoms for all patients with atrophic rhinitis.

6. B, pg. 669, irritant rhinitis is due to small airborne substances not typically categorized as allergens. These substances include volatile organic compounds (perfume, paint), particulates and smoke. Corrosive rhinitis results from exposure to such high concentration of chemical gases that inflammation and even mucosal ulceration develops. This includes ammonia and chlorine. Immunologic rhinitis is due to IgE directed against a substance at work, such as animal dander (veterinarian, livestock breeder) or grain flour (baker). Cytotoxic is not a category of work-related rhinitis.

7. A, pg. 665, increased sibling number and daycare are thought to be surrogates of frequent viral respiratory infections. These infections are thought to be protective because of skewing the T helper cells towards a non-allergic phenotype.

8. C, pg. 666, inflammation in the upper airway is associated with inflammation in the lower airway. Even without overt presence of asthma, many patients with nasal allergy have some airway hyperresponsiveness. Rhinitis has been associated with increased development of
asthma, not the reverse. Worsening rhinitis is associated with asthma exacerbations. About 80% of asthma patients have rhinitis symptoms.

9. D, pg. 666, circadian variations are present in all patients with highest levels of inflammation in the morning. Most patients are not non-specifically irritated by dust mites. Coffee is not associated with nasal congestion. A supine position may cause worsening congestion, but not always.

10. C, pg. 667, CT is the most accurate way to image the sinuses. Contrast is not needed unless evaluating vasculature. MRI and X-ray are less sensitive.
FIT Board Review Corner – November 2017
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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 42b (pages 672-685): Allergic and Nonallergic Rhinitis
Prepared by: Tammy Peng, MD

1. Increased levels of which of the following cytokine have been detected only during late phase response following allergen challenge experiments?
   a. IL-1β
   b. Tumor necrosis factor (TNF)- α
   c. IL-5
   d. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

2. Which cytokine is an important mast cell growth factor that promotes B-cell switching to the production of IgE?
   a. IL-5
   b. IL-4
   c. IL-33
   d. IL-13

3. Which of the following is a neuropeptide found in nasal mucosa that is secreted by unmyelinated nociceptive C fibers?
   a. Neuropeptide Y
   b. Vasoactive intestinal peptide (VIP)
   c. Peptide histidine-methionine
   d. Neurokinin A
4. Which of the following interventions is the most effective approach to removing indoor cat allergen?
   a. Tannic acid application
   b. Washing bedding
   c. Removing the cat from the indoor environment
   d. HEPA filter use

5. Which of the following medications are rapidly absorbed, provide relief within 1-2 hours and have been shown to reduce sneezing, itching, rhinorrhea and eye symptoms, but have limited efficacy in alleviating nasal congestion?
   a. Intranasal corticosteroids
   b. Leukotriene inhibitors
   c. Oral antihistamines
   d. Decongestants

6. Which of the following is the primary side effect of intranasal corticosteroids?
   a. Epistaxis
   b. Local nasal irritation
   c. Septal perforations
   d. Candida overgrowth

7. Which medications are effective in treatment of patients who complain predominantly of rhinorrhea, but have no effect on sneezing, itching or nasal congestion?
   a. Anticholinergics
   b. Antihistamines
   c. Decongestants
   d. Intranasal Corticosteroids

8. Which of the following intranasal corticosteroid sprays has been given a pregnancy category B rating?
   a. Beclomethasone
   b. Fluticasone propionate
   c. Mometasone furoate
   d. Budesonide
9. Which of the following medications used in the treatment of allergic rhinitis has a FDA pregnancy category C rating?
   a. Nasal cromolyn
   b. Olopatadine and azelastine
   c. Loratadine and cetirizine
   d. Diphenhydramine and chlorpheniramine

10. In addition to older-generation oral antihistamines, which medications should be avoided in treating rhinitis in elderly patients due to possible adverse effects on blood pressure, cardiac rhythm, central nervous system and the urinary tract?
    a. Intranasal corticosteroids
    b. Oral decongestants
    c. Leukotriene inhibitors
    d. Topical antihistamines
Answers

1. C, pg. 672 “Late Response to Allergen”
   Increased levels of IL-1β, TNF-α and GM-CSF have been detected in early hours after provocation in allergen challenge experiments. Increased levels of IL-5, IL-6, GM-CSF and TNF were detected during late phase response.

2. A, pg. 673 “Late Response to Allergen”
   IL-4 is an important mast cell growth factor and promotes switching of B cells to IgE production. IL-13 shares most functions with IL-4 and may contribute to late phase inflammation and symptoms of allergic rhinitis. IL-33, in addition to IL-25 and thymic stromal lymphopoietin (TSLP), is a epithelium-derived cytokine that has been identified and found to have an important role in development and perpetuation of allergic rhinitis.

3. D, pg. 673 “Neurogenic Activity”
   Neuropeptides secreted by unmyelinated nociceptive C fibers include neurokinin A, calcitonin gene-related peptide (CGRP), gastrin releasing peptide and tachykinins. Neuropeptides secreted by parasympathetic nerve endings are vasoactive intestinal peptide (VIP) and peptide histidine-methionine. Neuropeptide Y is secreted by sympathetic nerve endings.

4. C, pg. 676 “Allergen Avoidance Measures”
   The most effective approach to reduction of indoor cat allergen is removal of the cat from the indoor environment. However, this may not immediately be effective because residual allergen may remain relatively high in carpeting and upholstered furniture for several months or longer. After removal of cat, carpeting should be taken up and upholstered furniture should be cleaned. One study has also demonstrated that several measures including removal of carpeting, tannic acid application, washing bedding and washing the cat leads to reduction of Fel D 1 levels in the house.

5. C, pg. 676 “Antihistamines”
   Oral antihistamines have been shown to reduce histamine-mediated symptoms such as sneezing, itching, rhinorrhea and eye symptoms, but are not as effective in treating nasal congestion. Oral antihistamines are rapidly absorbed and begin to provide relief within 1-2 hours. Intranasal corticosteroids begin to have effects within 7 to 8 hours of dosing. Decongestants reduce nasal congestion but have no other effects on symptoms of rhinitis.
Local nasal irritation is the principal side effect of intranasal corticosteroids, occurring in approximately 10% of patients. Incidence of epistaxis during two weeks of use ranges from 4-8% depending on different formulations. Septal perforations and *Candida* overgrowth have been rarely reported.

7. A, pg. 678 “Anticholinergics”
Anticholinergic drugs are useful in patients whom rhinorrhea is the predominant complaint. Ipratropium bromide is one anticholinergic that can be administered intranasally and shown to be effective on controlling watery nasal discharge in perennial allergic rhinitis with no effect on sneezing, itching or nasal congestion.

8. D, pg. 679 “Pregnancy”
Most intranasal corticosteroids are given a FDA pregnancy category C rating, with the exception of budesonide, which has a pregnancy category B rating. If a patient is already being treated with an intranasal corticosteroid and her rhinitis is well-controlled, continuation of current therapy is reasonable as gestational risk has not been confirmed in observational human data and reported safety data on all available compounds are reassuring. When intranasal corticosteroid therapy is being started during pregnancy, budesonide is often the drug of choice because of its category B rating.

Topical antihistamines such as olapatadine and azelastine do not have long history of use in pregnancy and have FDA pregnancy category C ratings. Nasal cromolyn, up to one spray 4-6 times daily can be used in pregnancy with an excellent safety profile and FDA pregnancy category B rating. Both diphenhydramine and chlorpheniramine have a long record of use in pregnancy and are FDA pregnancy category B. However, given central nervous system and anticholinergic effects, these two medications may be difficult to tolerate. Loratadine and cetirizine have been extensively studied in pregnancy and both have a FDA pregnancy category B rating.

Oral decongestants should be avoided in treatment of rhinitis in elderly patients due to adverse effects including hypertension, extrasystoles, arrhythmias, insomnia, agitation and urinary tract obstruction. Older-generation antihistamines should be avoided because of their sedating
and anticholinergic effects. It is important to note that although intranasal corticosteroids are generally safe, they may cause more bleeding in the older population due to increased fragility of the nasal mucous membranes.
FIT Board Review Corner – December 2017
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Middleton Chapter 43 (pages 686-692) Rhinosinusitis and Nasal Polyps
Prepared by: Malika Gupta, MD

1. Increased symptoms of rhinosinusitis should be present for how long before it can be called chronic?
   a. 21 days
   b. 8 weeks
   c. 12 weeks
   d. Does not depend on duration of symptoms.

2. Viral infections of the nose increase the risk of bacterial superinfection. What percent of acute viral upper respiratory tract infections develop bacterial superinfection?
   a. 0.5% - 2%
   b. 10% - 20%
   c. 33%
   d. 90%

3. Which of the following is true of acute rhinosinusitis (ARS)?
   a. ARS is sudden in onset
   b. An episode should not last beyond 3 weeks
   c. Symptoms may persist after adequate treatment
   d. ARS is defined by symptoms and clinical findings consistent with ARS, with more than 3 episodes per year
4. Which is true of the association between asthma and sinusitis?
   a. Only up to 25% of patients with asthma also present with sinusitis.
   b. Drug management of sinusitis or sinus surgery does not cause any change in asthma symptoms.
   c. Drug management of sinusitis or sinus surgery does not cause any change in asthma symptoms.
   d. Up to 70% of patients with asthma also present with sinusitis as confirmed on sinus x-ray examination.

5. Choose the correct option regarding imaging in the diagnosis of sinusitis.
   a. Sinus radiographs are the imaging modality of choice in the diagnosis of both ARS and CRS.
   b. There is no condition in which ultrasound imaging may be used in diagnosis.
   c. The radiation risk associated with CT scanning prevents it from being used in the diagnosis of CRS.
   d. Magnetic resonance imaging (MRI) is sensitive for the evaluation of fungal sinusitis and extension of disease into the brain.

6. Which is true of the pathophysiology of CRS?
   a. Eosinophilia is a hallmark of CRS in the absence of polyp formation (CRSsNP).
   b. The typical cytokine pattern of CRSsNP disease consists of proinflammatory and neutrophil-associated cytokines including interleukin (IL)-1β.
   c. The typical cytokine pattern of CRSwNP disease consists of proinflammatory and neutrophil-associated cytokines including interleukin (IL)-1β.
   d. CRSsNP is characterized by a Th2-dominated cytokine pattern with high IL-5.

7. Which of the following is the most frequent bacteria associated with acute sinusitis?
   a. *Streptococcus pneumoniae*
   b. *Streptococcus pyogenes*
   c. *Staphylococcus aureus*
   d. *Staphylococcus epidermidis*

8. Which of these is not a typical complication of FESS?
   a. Severe bleeding
   b. Orbital trauma
   c. Paralysis
d. Cerebrospinal fluid leaks

9. Which is true about the epidemiology of CRSwNP?
   a. Nasal polyps do not occur more frequently in asthma patients with aspirin sensitivity.
   b. Nasal polyps do not occur more frequently in patients with cystic fibrosis.
   c. Early-onset allergic asthma is significantly more frequently linked to polyps compared with nonallergic late-onset asthma.
   d. When polyps occur in children and adolescents, CF should always be considered.

10. Which of the following is a characteristic of aspirin-exacerbated respiratory disease (AERD)?
   a. Low blood eosinophil counts
   b. An increase of neutrophils in the nasal mucosa
   c. An increase of eosinophils in the bronchial mucosa
   d. Elevated cysteinyl-leukotriene concentrations in the tissue and urine, which decreases after aspirin exposure.
Answers

1. C, pg. 686
   “A clinical definition of rhinosinusitis was proposed and since refined by a working group of European otolaryngologists and is now internationally accepted (i.e., EPOS 2012). This definition states that the diagnosis of rhinosinusitis is based on symptoms and their duration but also includes endoscopic and/or radiologic criteria. Symptoms must be present for at least 12 weeks to differentiate chronic rhinosinusitis (CRS) from acute rhinosinusitis (ARS).”

2. A, pg. 687
   IL-4 is “Acute bacterial rhinosinusitis is considered a complication of acute viral rhinosinusitis. Viral infections of the nose and sinuses induce multiple changes in the nose, which increase the risk for bacterial superinfection. These changes include epithelial damage and mechanical, humoral, and cellular defenses, e.g., macrophages. However, bacterial superinfection is limited to 0.5% 2% of acute viral upper respiratory tract infections.”

3. A, pg. 688
   “ARS is sudden in onset, and each episode may last up to 12 weeks. If symptoms of a common cold worsen after 5 days of onset, or persist for longer than 10 days, and are more prolonged and/or severe than normally experienced with a viral infection, the diagnosis of ARS, either viral or bacterial, is probable. Symptoms should resolve completely after adequate treatment. Recurrent ARS is defined by symptoms and clinical findings consistent with ARS, with more than 4 episodes per year. Each episode may last up to 12 weeks. Between episodes, symptoms are absent without the use of concurrent antibiotic therapy.”

4. D, pg. 688
   “Up to 70% of patients with asthma also present with sinusitis as confirmed on sinus x-ray examination. Furthermore, strong circumstantial evidence suggests that CRS may be linked to chronic lung disease, especially severe asthma. As reported in different studies, radiographic
sinus abnormalities are frequently found in children and adults with asthma exacerbations, and drug management of sinusitis or sinus surgery results in significant improvement in asthma symptoms and exacerbations and in reduction of corticosteroid use for asthma. The mechanisms by which sinusitis influences asthma, however, are not well understood.

5. D, pg. 688
“Standard sinus radiographs may be used for the diagnosis of acute frontal or maxillary sinusitis but often do not provide additional information over history alone. Ultrasound imaging is of limited value but may be used in pregnant women to avoid exposure to radiation. CT helps to define the extent of the disease, anatomic abnormalities, and changes in the ostiomeatal complex and provides a “map” for surgery. CT also is indicated for evaluation of orbital or cerebral complications of sinusitis, for the preoperative evaluation of chronic sinusitis, and in the diagnosis of all sinister pathologic entities such as tumor, meningocoeles, or mucoceles. Magnetic resonance imaging (MRI) is particularly sensitive for the evaluation of fungal sinusitis and extension of disease into the brain.”

6. B, pg. 690
“In a study evaluating the percentage of eosinophils (of 1000 inflammatory cells counted per vision field), less than 10% were eosinophils (overall mean, 2%) in 31 patients with untreated CRSsNP, whereas in 123 with untreated CRSwNP, 108 samples showed more than 10% eosinophils (overall mean, 50%). These observations suggest that tissue eosinophilia is not a hallmark of chronic sinusitis in the absence of polyp formation. The typical cytokine pattern of CRSsNP disease consists of proinflammatory and neutrophil-associated cytokines including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-8, resulting in increased neutrophil activation (myeloperoxidase [MPO]). In contrast with CRSwNP, which is characterized by an eosinophil-rich Th2-dominated cytokine pattern with high IL-5 and low TGF-β concentrations, CRS shows a Th1-biased immune response with high interferon (IFN)-γ and an elevated TGF-β signal.”

7. A, pg. 690
"With *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* representing the most frequent bacteria associated with acute sinusitis, first-choice antibiotics include amoxicillin, second-generation cephalosporins, or eventually amoxicillin plus clavulanic acid; in penicillin-allergic subjects, alternative choices include trimethoprim-sulfamethoxasole, azithromycin, and clarithromycin."

8. C, pg. 691
   “Possible complications of FESS include severe bleeding, orbital trauma, and cerebrospinal fluid leaks, with secondary complications such as meningitis or cerebral damage; however, in experienced hands, complications are not more frequent with endonasal approaches than with the former open procedures.”

9. D, pg. 691
   “Nasal polyps occur more frequently in asthma patients with aspirin sensitivity, and CF.” (Ref: Settipane GA: Epidemiology of nasal polyps. Allergy Asthma Proc. 17:231-236 1996)
   “Asthma frequently coincides with CRSwNP, and nonallergic late-onset asthma is significantly more frequently linked to polyps compared with early-onset allergic asthma.”
   “In a large series of patients with CF, mainly neutrophilic nasal polyposis was noted in 37% to 48%. When polyps occur in children and adolescents, CF should always be considered.”

10. C, pg. 692
    OThe full typical clinical picture of aspirin-exacerbated respiratory disease (AERD) is characterized by increased blood eosinophil counts, an increase of eosinophils in the nasal and bronchial mucosa, and elevated cysteinyl-leukotriene concentrations in the tissue and urine, which further increases after aspirin exposure.”