**Allergy and Immunology Review Corner:** Chapter 91 of *Middleton’s Allergy Principles and Practice, 7th Edition*, edited by N. Franklin Adkinson, et al.

**Chapter 91: Cholinergic Mechanisms and Anticholinergic Therapy**

*Prepared by Paul Keiser, MD, Walter Reed Army Medical Center, and Sarah Bozeman, DO, University of Mississippi*

1. Based on animal models, what aspect of eosinophil migration correlates with airway hyperreactivity?
   A. Total eosinophil count in BAL.
   B. Percentage of activated eosinophils in BAL.
   C. Number of eosinophils in lung parenchyma.
   D. The presence of activated eosinophils near airway smooth muscle cells.
   E. The presence of activated eosinophils around nerves.

2. One potential advantage of tiotropium over ipratropium in treating COPD is due to:
   A. Decreased affinity for M2 receptors
   B. Decreased affinity for M3 receptors
   C. More rapid dissociation from M1 receptors
   D. More rapid dissociation from M2 receptors
   E. Faster onset of action

3. Treatment with anticholinergic drugs has been shown to improve which of the following types of asthma exacerbations?
   A. Psychogenic asthma
   B. Nocturnal asthma
   C. Allergic asthma
   D. Asthma caused by beta blockers
   E. All of the above.

4. Which of these classes of commonly prescribed drugs has potent anticholinergic effects?
   A. Non-steroidal anti-inflammatory drugs
   B. Macrolide antibiotics
   C. Leukotriene inhibitors
   D. Chromones
   E. Antihistamines.

5. Compared with treatment with beta-agonist alone, treatment of severe acute asthma in children and adolescents with combination beta-agonist and anticholinergic inhaled medications is associated with:
   A. Decreased risk of hospitalization
   B. Decreased short-term improvement in FEV1
   C. Increased incidence of nausea or vomiting
   D. Increased incidence of tremor
E. All of the above

6. Airway smooth muscle has both M2 and M3 receptors. What other tissue or cell has M2 receptors?
   A. Neutrophils
   B. Mast cells
   C. Glands
   D. Parasympathetic Ganglia

7. Eosinophil activation takes place in the lungs upon several events. Which of the following is not one of those?
   A. Inhalation of antigens by a sensitized animal
   B. Treatment with short-acting beta agonists
   C. Ozone exposure
   D. Exposure to organophosphates

8. Ipratropium bromide increases PEF rate in asthmatic patients. The maximum increase of 45L/min is achieved at 500μg. Which of the following is the clinically used dose and the typical resulting increase in PEF?
   A. 36μg and 10L
   B. 100μg and 20L
   C. 254μg and 30L
   D. 425μg and 40L

9. In which situation, are the use of anti-cholinergics of questionable benefit?
   A. Asthmatic patients who do not tolerate SABA
   B. Patients with bronchoconstriction secondary to Beta-blockers
   C. EIA
   D. Patients with COPD

10. What is the ½ life (time to 50% recovery of response) of tiotropium and ipratropium respectively?
    A. 1h, 30min
    B. 9h, 80min
    C. 6h, 4h
    D. 12h, 145min

Answers
1. D, page 1606
   “It is important to note that it is not eosinophil number in the BAL or lung tissue that determines hyperreactivity, but the specific location of eosinophils within the lungs, i.e. around nerves, that causes hyperreactivity… Mechanisms for loss of neuronal M2 function in human disease are not known, but a role for eosinophils is suggested because of the significant increase in eosinophils associated with nerves in sections of human lung from fatal asthma... Studies testing whether treatments that interfere with eosinophil
migration to the lung prevent airway hyperreactivity cannot be considered conclusive unless the specific presence of eosinophils around airway nerves is evaluated.”

2. D, page 1608
“The major advantages of this medication, over ipratropium, are its long duration of action (9 h for 50% recovery of the response vs 81.2 min) and its pharmacokinetic selectivity for M3 receptors. While it binds to M2 and M3 receptors with approximately equal affinity, it dissociates from M2 receptors nearly 10 times faster than from M3 receptors (T1/2 3.6 h for M2 vs T1/2 34.7 h for M3). Furthermore, tiotropium dissociates from M1 and M3 receptors 100 times more slowly than ipratropium. The onset of action to achieve 50% maximum bronchodilation is 34.8 min compared with 7.6 min for ipratropium.

3. E, page 1611
Patients with a major psychogenic component to their asthma respond better to ipratropium than other patients. Intravenous atropine (30μg/kg) almost completely attenuates the decrease in peak flow at night in patients with nocturnal asthma, indicating that nocturnal asthma is mediated by a cholinergic reflex. In atopic asthmatics, antigen-induced increases in airway resistance are completely blocked by intravenous atropine (1.5–2.5 mg) or inhaled atropine (1.5 mg). Similar findings have been reported using ipratropium bromide and oxitropium bromide. Several studies have shown that both intravenous and inhaled atropine provide partial protection against exercise-induced asthma.

4. E, page 1614
“Many antihistamines (including diphenhydramine and desloratadine) are potent anticholinergics, binding to M3 receptors with affinities that are often comparable to their affinities for H1 receptors.”

5. A, page 1612
“A review of 10 randomized controlled trials in children and adolescents treated for acute asthma, compared results of trials using either single or multiple doses of inhaled anticholinergics in combination with β-agonists. Combination therapy resulted in significant improvement in lung function and a 30% reduction in the risk of hospitalization in the subset of studies using multiple anticholinergic dose protocols.”

6. D, page 1605
Legend to figure 91.1: “In the lungs, muscarinic receptors are found on airway smooth muscle (M3/M2), epithelium (M3), glands (M3), parasympathetic ganglia (M1/M2), parasympathetic nerve endings (M2), and in inflammatory cells, mast cells (M1), macrophages (M3), neutrophils (M4/M5), and eosinophils (M3/M4).”
Also see page 1606: “Release of acetylcholine from postganglionic parasympathetic nerves is tightly controlled by inhibitory M2 muscarinic receptors on nerves. The neuronal receptors were initially classified as ‘cardiac-like’ muscarinic receptors, and ultimately designated M2 when cardiac receptors were classified as M2. M2 muscarinic receptors have subsequently been shown to inhibit acetylcholine release from
parasympathetic nerves in every mammalian species examined thus far, including humans and mice. In addition to parasympathetic control of muscle, M2 receptors also inhibit acetylcholine release from parasympathetic nerves supplying glands.”

7. B, page 1606
“Eosinophil activation takes place when sensitized animals inhale antigen, are infected with virus, are exposed to ozone or exposed to organophosphate pesticides.”

8. A, page 1610
Legend to figure 91.4: “The maximum increase, 45L/min, is achieved at 500 μg. In contrast, the clinically used dose, 36μg (arrow), increased peak expiratory flow rate only 10L/min. Consistent use of these small doses has led to the impression that anticholinergics are not effective in asthma and subsequently to the underestimation of a parasympathetic role in asthma.”

9. C, page 1612
“The National Heart, Lung, and Blood Institute, Expert Panel Report No. 3: Guidelines for the Diagnosis and Management of Asthma, published in 2007, revised the previous dismissive assessment of anticholinergics in the treatment of asthma… Their opinion on the role of anticholinergics in exercise-induced asthma is mixed, at one point stating that ipratropium does not block exercise-induced asthma, and elsewhere stating that anticholinergics attenuate exerciseinduced asthma, though not as completely as other medications.”
See also page 1611:
“A recent meta-analysis of studies addressing treatment of exercise induce bronchospasm concluded that β-agonists, anticholinergics, and mast cell stabilizers all gave significant protection, and that there were substantial differences among patients in which medication was most efficacious… [D]ifferences among patients in responsiveness to anticholinergic treatment can be related to differences in vagal activity.”

10. B, page 1608
One “major advantage of [tiotropium], over ipratropium, [is] its long duration of action (9 h for 50% recovery of the response vs 81.2min).”

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**Chapter 92:** Antileukotriene Therapy

*Prepared by John Seyerle, MD, Ohio State University*

1. What is created using phospholipase A2?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
2. What is created using 5-lipoxygenase?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
   C. Leukotriene A4
   D. Cysteinyl leukotrienes
   E. Leukotriene B4

3. What is converted to Leukotriene C4 by LTC4 Synthase?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
   C. Leukotriene A4
   D. Cysteinyl leukotrienes
   E. Leukotriene B4

4. What is created using Leukotriene A4 Hydrolase?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
   C. Leukotriene A4
   D. Cysteinyl leukotrienes
   E. Leukotriene B4

5. Cyclooxygenase converts arachidonic acid to what product?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
   C. Leukotriene A4
   D. Cysteinyl leukotrienes
   E. Leukotriene B4

6. Gamma-glutamyl transpeptidase assists in the conversion to what product?
   A. LTA4
   B. LTB4
   C. LTC4
   D. LTD4
   E. LTE4

7. 5-LO inhibitors block the conversion of what product?
   A. Arachidonic acid
   B. Prostaglandins and thromboxanes
   C. Leukotriene A4
   D. Cysteinyl leukotrienes
   E. Leukotriene B4
8. Which of the following blocks the production of Leukotriene B4?
   A. Cyclooxygenase
   B. 5-LO inhibitors
   C. LTA4 Hydrolase
   D. Cys LT receptor antagonists
   E. LTC4 Synthase

9. What possible problem is most concerning in asthmatic patients weaned off oral steroids after starting zafirlukast?
   A. Elevated liver transaminases
   B. Elevated theophylline levels
   C. Elevated warfarin levels
   D. Churg-Strauss syndrome

10. Which of the following groups would have the highest level of baseline LTC4 found in bronchoalveolar lavage?
    A. Non-atopic, nonasthmatics
    B. Atopic non-asthmatics
    C. Non-atopic asthmatics
    D. Atopic asthmatics

Answers
1. A, page 1620
   Phospholipase A2 converts membrane hospholipids to arachidonic acid.

2. C, page 1620
   5-lipoxygenase converts arachidonic acid to leukotriene A4.

3. C, page 1620
   LTC4 synthase converts Leukotriene A4 to Leukotriene C4, the first of the cysteinyl leukotrienes.

4. E, page 1620

5. B, page 1620
   Cyclooxygenase converts arachidonic acid to prostaglandins and thromboxanes.

6. D, page 1620
   Gamma-glutamyl transpeptidase converts LTC4 to LTD4.

7. A, page 1620
   5-LO inhibitors, such as Zileuton, block the conversion of arachidonic acid to Leukotriene A4.

8. B, page 1620
5-LO inhibitors block the conversion of arachidonic acid to Leukotriene A4, thereby blocking production of both Leukotriene B4 and the cysteinyl leukotrienes.

9. D, page 1629
While elevated liver transaminases, elevated theophylline levels, or elevated warfarin levels are possible effects of zarfirlukast, the most concerning condition would be Churg-Strauss, a rare eosinophilic vasculitis.

10. D, page 1622
Bronchoalveolar lavage fluids showed significant levels of LTC4 only in atopic asthmatics.