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Dyspnea, hypotension, and tachycardia soon after administration of  $\beta$ -lactam antibiotics are suggestive of anaphylactic shock. Hypotension occurs in anaphylactic shock secondary to collapse of peripheral vascular resistance, increases in vascular permeability, and leakage of capillary fluid. Stimulation of the smooth muscle tone within the bronchial wall, along with an increase in bronchial secretion, accounts for the dyspnea seen in anaphylaxis. Skin symptoms (urticaria and angioedema) may occur secondary to vasodilatation and increased vascular permeability of skin capillaries. Increases in GI smooth muscle tone may result in vomiting, abdominal cramps, and diarrhea.

Epinephrine is the drug of choice for the treatment of anaphylactic shock due to its ability to reverse all of the pathophysiologic mechanisms of anaphylaxis. Stimulation of  $\alpha_1$  receptors counteracts the vasodilatation of cutaneous and viscera vasculature, thus increasing blood pressure. Epinephrine-mediated increases in cardiac contractility ( $\beta_1$  effect) and cardiac output also increase blood pressure and improve peripheral perfusion.

Epinephrine-induced stimulation of  $\beta_2$  receptors results in bronchodilatation, making it also a popular choice for the treatment of severe asthmatic reactions.

**(Choice A)** Steroids inhibit inflammation by reducing capillary permeability and suppressing neutrophil activity. Steroids also inhibit phospholipase A2, resulting in decreased formation of prostaglandin inflammatory mediators. Because steroids anti-inflammatory effects are not acute, they are not effective in the acute treatment of life-threatening anaphylaxis. Epinephrine should be given prior to steroids and antihistamines in the treatment of anaphylaxis.

**(Choice C)** Norepinephrine has a predominantly alpha-1 adrenergic effect; thus, it can cause intense vasoconstriction, which may limit cardiac output. Furthermore, it has little effect on the beta-2 adrenoceptor, so it has little or no bronchodilator action.

**(Choice D)** Dobutamine is a synthetic drug with primary beta-1 adrenergic action



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contractility ( $\beta_1$  effect) and cardiac output also increase blood pressure and improve peripheral perfusion.

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**(Choice A)** Steroids inhibit inflammation by reducing capillary permeability and suppressing neutrophil activity. Steroids also inhibit phospholipase A2, resulting in decreased formation of prostaglandin inflammatory mediators. Because steroids anti-inflammatory effects are not acute, they are not effective in the acute treatment of life-threatening anaphylaxis. Epinephrine should be given prior to steroids and antihistamines in the treatment of anaphylaxis.

**(Choice C)** Norepinephrine has a predominantly alpha-1 adrenergic effect; thus, it can cause intense vasoconstriction, which may limit cardiac output. Furthermore, it has little effect on the beta-2 adrenoceptor, so it has little or no bronchodilator action.

**(Choice D)** Dobutamine is a synthetic drug with primary beta-1 adrenergic action that can cause an increased cardiac output without the other effects of epinephrine.

**(Choice E)** Diphenhydramine is a first generation antihistamine drug that competitively inhibits peripheral H1 receptors in the GI tract, blood vessels, and respiratory tract. Diphenhydramine may be used for the treatment of anaphylaxis after the patient is stabilized with epinephrine.

#### Educational Objective:

Anaphylactic shock is characterized by vasodilatation, increased vascular permeability, and bronchoconstriction. Epinephrine counteracts these physiological mechanisms and is the drug of choice for the treatment of anaphylaxis.



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The following vignette applies to the next 2 items. The items in the set must be answered in sequential order.

Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 52-year-old woman comes to the emergency department with pain and redness affecting her left leg. The patient's symptoms began 2 days ago and have progressed to the point where she cannot walk without experiencing severe pain. Physical examination shows a large, erythematous area with indistinct margins over her left leg. The area feels hot and indurated and is exquisitely tender. She is admitted to the hospital for severe left leg cellulitis and is started on intravenous cefazolin. Several minutes after the infusion is started, she experiences shortness of breath, diffuse itching, and dizziness. Her blood pressure is 64/38 mm Hg and heart rate is 130/min. On examination, there is a diffuse erythematous skin rash and bilateral wheezing is heard on lung auscultation.

### Item 1 of 2

Which of the following is most likely to be elevated in this patient's serum as a result of her medication reaction?

- A. Alkaline phosphatase (14%)
- B. Calcitonin (5%)
- C. Collagenase (8%)
- D. Myeloperoxidase (32%)
- E. Tryptase (38%)

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Anaphylaxis	
Triggers	<ul style="list-style-type: none"><li>• Immune mediated (eg, medications, food, insect stings)</li><li>• Nonimmune mediated (eg, intravenous contrast, mast cell activation syndrome)</li></ul>
Clinical manifestations	<ul style="list-style-type: none"><li>• Cardiovascular<ul style="list-style-type: none"><li>◦ Vasodilation → hypotension &amp; tissue edema</li><li>◦ Tachycardia</li></ul></li><li>• Respiratory<ul style="list-style-type: none"><li>◦ Upper airway edema → stridor &amp; hoarseness</li><li>◦ Bronchospasm → wheezing</li></ul></li><li>• Cutaneous<ul style="list-style-type: none"><li>◦ Urticarial rash, pruritus, flushing</li></ul></li><li>• Gastrointestinal<ul style="list-style-type: none"><li>◦ Nausea, vomiting, abdominal pain</li></ul></li></ul>
Treatment	<ul style="list-style-type: none"><li>• Intramuscular epinephrine</li></ul>

This patient is experiencing an **anaphylactic reaction** to the cephalosporin cefazolin. Anaphylaxis is a systemic type I hypersensitivity reaction characterized by increased vascular permeability and **multisystem edema**, leading to massive shifting of intravascular fluid to the extravascular compartment. Symptoms often begin within seconds to minutes after intravascular exposure to an inciting factor (eg, insect stings, intravenous medications) but can take up to 2 hours to develop with orally ingested antigens.

Anaphylaxis results from widespread **mast cell and basophil degranulation** and resultant **histamine** and



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Anaphylaxis results from widespread **mast cell and basophil degranulation** and resultant **histamine** and **tryptase** release. Tryptase is an enzyme that is relatively specific to mast cells, and elevated serum levels of tryptase are often used to support a clinical diagnosis of anaphylaxis after the patient has been stabilized.

**(Choice A)** Alkaline phosphatase is present in all cells of the body, but the highest levels are found in the liver, bones, and placenta.

**(Choice B)** Calcitonin is produced by the C cells of the thyroid gland and can be useful as a tumor marker for medullary thyroid carcinoma.

**(Choices C and D)** Collagenases breakdown collagen. Myeloperoxidase catalyzes formation of hypochlorous acid (ie, bleach) during the oxidative burst in the immune response to infection. These enzymes are found predominantly in neutrophils and are not significantly elevated during an acute allergic reaction.

#### Educational objective:

Anaphylaxis is the result of widespread mast cell and basophil degranulation and the release of preformed inflammatory mediators, including histamine and tryptase. Tryptase is relatively specific to mast cells and can be used as a marker for mast cell activation.

Immunology

Subject

Allergy &amp; Immunology

System

Anaphylaxis

Topic

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Item 2 of 2

The patient's anaphylactic reaction is determined to be mediated by antigen-specific IgE antibodies attached to high-affinity receptors on the surface of mast cells and basophils. Which of the following mechanisms is most likely to trigger vasoactive substance release by these cells?

- A. Antibody-receptor covalent binding (49%)
- B. Antibody-receptor dissociation (3%)
- C. Receptor aggregation (33%)
- D. Receptor detachment from the cell surface (4%)
- E. Receptor internalization (10%)

Omitted  
Correct answer  
C

33% Answered correctly

04 secs Time Spent

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### Explanation

#### High-affinity IgE receptor activation



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### High-affinity IgE receptor activation

The diagram illustrates the process of high-affinity IgE receptor activation. On the left, a mast cell is shown with several green Y-shaped IgE molecules bound to its surface. These IgE molecules are bound to a large, brown, branched multivalent antigen. The mast cell contains internal structures labeled 'Secretory granules'. An arrow points from this initial state to the right, where the mast cell is shown in a more active state. The green IgE molecules are now aggregated together on the cell surface, a process labeled 'Receptor aggregation'. Small white dots are seen leaking from the cell, labeled 'Degranulation', indicating the release of secretory granules.

The **high-affinity IgE receptor** (Fc $\epsilon$ RI) is found on mast cells and basophils and plays a primary role in mediating the allergic response. The receptor normally binds the Fc portion of circulating IgE, coating the cell with various antigen-specific IgE molecules. When a multivalent antigen comes in contact with the cell, multiple IgE antibodies become **cross-linked**, resulting in **aggregation** of the Fc $\epsilon$ RI receptors on the mast cell surface. This clumping of receptors leads to the activation of non-receptor tyrosine kinases, triggering an intracellular cascade that ultimately results in mast cell and basophil **degranulation**.

(Choices A and B) The high strength of the IgE-Fc $\epsilon$ RI bond is a result of the sum of many weak noncovalent



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**(Choices A and B)** The high strength of the IgE-Fc $\epsilon$ RI bond is a result of the sum of many weak noncovalent forces; it is not associated with the formation of covalent (eg, disulfide, peptide) bonds. The strength of this attachment is such that antibody-receptor dissociation is rare; most of the total IgE in the body is bound to the surface of mast cells and basophils and not circulating freely.

**(Choice D)** Receptor detachment from the cell surface is not a known mechanism of signal transduction.

**(Choice E)** Receptor internalization occurs in the process of synaptic desensitization to excessive neurotransmitter stimulation. It also occurs in receptor-mediated endocytosis of substances such as iron (ie, transferrin receptor) and cholesterol (ie, LDL receptor).

### Educational objective:

The high-affinity IgE receptor (Fc $\epsilon$ RI) is found on the surface of mast cells and basophils and normally binds the Fc portion of circulating IgE antibodies. Cross-linking of multiple membrane-bound IgE antibodies by a multivalent antigen results in aggregation of the Fc $\epsilon$ RI receptors, causing degranulation and the release of preformed mediators (eg, histamine, tryptase) that initiate an allergic response.

Immunology

Subject

Allergy &amp; Immunology

System

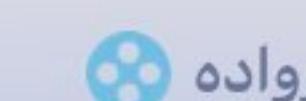
Anaphylaxis

Topic



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A 42-year-old woman is hospitalized due to fever and chills after a hemodialysis session. The patient has a history of end-stage kidney disease due to IgA nephropathy and recently began intermittent dialysis through a tunneled catheter. Medical history includes depression, for which she takes citalopram. Temperature is 38.4 C (101.1 F), blood pressure is 130/80 mm Hg, and pulse is 94/min. There is no erythema or tenderness at the catheter site, and the remainder of the physical examination shows no abnormalities. Blood cultures are obtained, and empiric vancomycin and ceftazidime are initiated. While receiving the intravenous vancomycin infusion, the patient reports a burning, itching sensation. Vital signs are unchanged, but repeat examination shows an erythematous rash involving the face and neck. She reports no history of drug allergy but has never received these antibiotics. Which of the following is the most likely underlying cause of this patient's current condition?

- A. Bacterial product release (2%)
- B. Cross-reacting antibodies (5%)
- C. Direct mast cell activation (85%)
- D. Drug-specific antibodies (3%)
- E. Serotonergic drug interaction (3%)

Omitted

Correct answer

C



85%

Answered correctly



02 secs

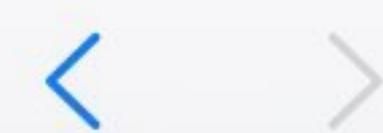
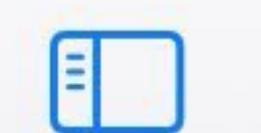
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Explanation



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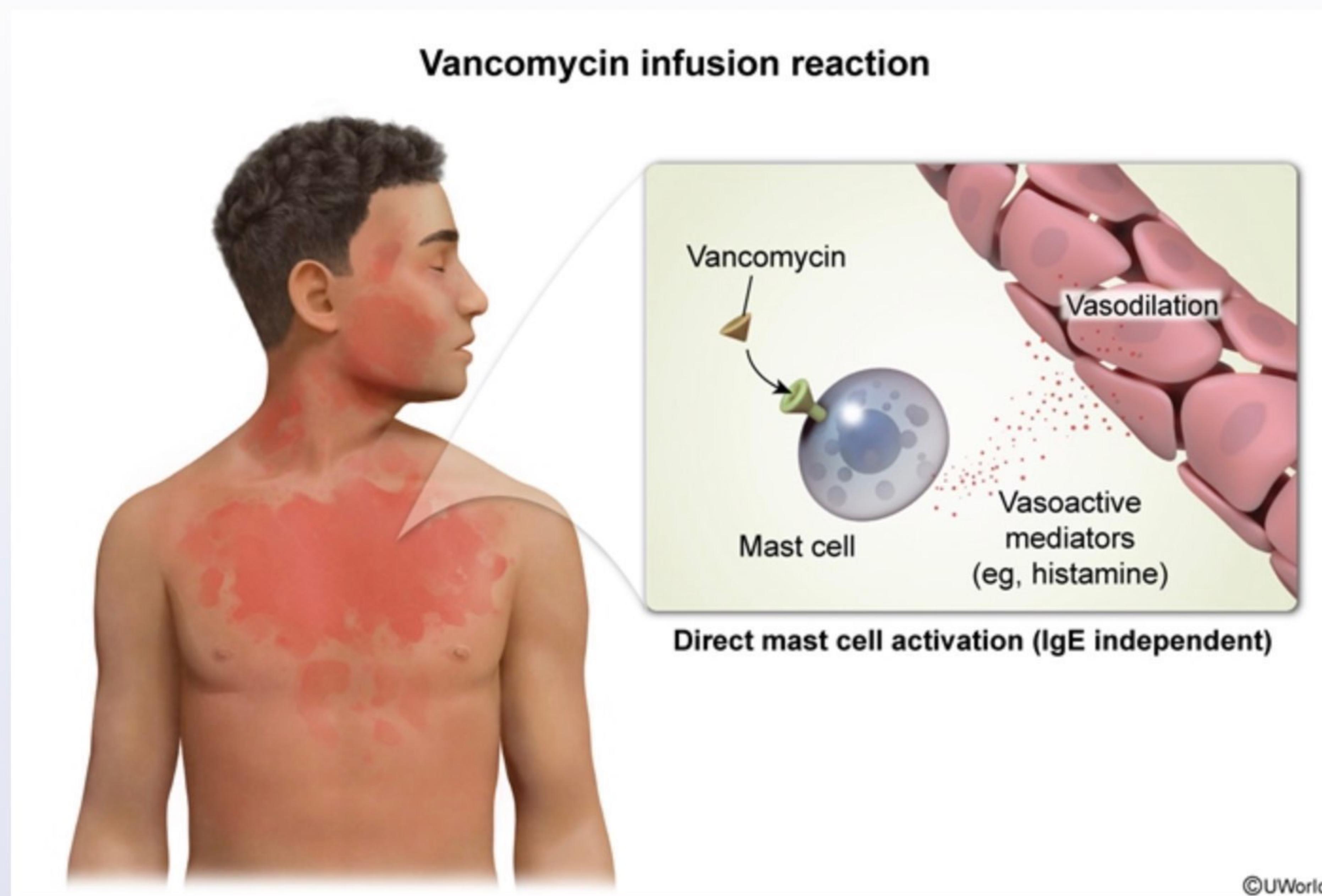
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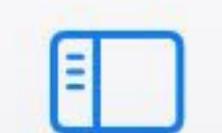
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This patient was given vancomycin and shortly thereafter developed burning, itching, and an erythematous rash on the face and neck, raising strong suspicion for **vancomycin infusion reaction (VIR)**. VIR is a **nonallergic reaction** that occurs when vancomycin is infused too **rapidly**; rapid vancomycin infusion can **directly activate mast cells**, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of VIR include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and



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**mast cells**, leading to the release of potent vasoactive mediators (eg, **histamine**).

Manifestations of VIR include flushing, pruritus, and an erythematous rash, which is usually seen on the upper torso, neck, and face. Myalgias and hypotension can occasionally occur. Discontinuation of the vancomycin and administration of diphenhydramine are usually curative. Because VIR is **not IgE mediated**, it is not a true allergic reaction, so vancomycin infusion can be resumed at a **slower rate** once symptoms resolve.

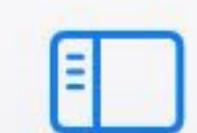
**(Choice A)** Patients with spirochetal illness (eg, syphilis, Lyme disease) can develop the Jarisch-Herxheimer reaction after the initiation of antimicrobial therapy. It is caused by massive release of bacterial products into the circulation due to widespread bacterial lysis. However, most cases arise several hours (not minutes) after antimicrobial therapy and are marked by high fever and worsened constitutional symptoms (eg, headache, myalgia).

**(Choices B and D)** Antibody-mediated drug reactions generally require previous exposure (sensitization) to the medication. This patient who has never received vancomycin is unlikely to have an antibody-mediated reaction; furthermore, such reactions are rare with vancomycin and are usually marked by urticaria, pruritus, hypotension, and angioedema.

**(Choice E)** Serotonergic drug interactions are most common with drugs that affect the serotonin system such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and certain antiemetics (eg, ondansetron). However, most cases are marked by alterations in autonomic function (eg, hypertension, tachycardia, hyperthermia), and rash is unusual.

#### Educational objective:

Vancomycin infusion reaction (flushing, pruritus, erythematous rash) is the most common adverse reaction to vancomycin. It occurs due to rapid vancomycin infusion, which leads to the direct activation of mast cells (non-IgE mediated) and the subsequent release of vasoactive mediators.



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A 1-year-old boy is brought to the office for a health maintenance visit. He has had no significant health issues and is growing well. The patient is up to date with recommended vaccinations and has had no prior vaccine-related adverse events. He has no known allergies. Physical examination shows no abnormalities. The patient receives the first dose of the subcutaneous measles-mumps-rubella vaccine. The next day, his mother calls the office because the patient has a temperature of 38 C (100.4 F) and has been irritable since the vaccination. The immunization site is mildly red, swollen, and tender; there is no other skin rash. Which of the following cells and effector mechanisms is most likely involved in pathogenesis of this patient's current condition?

- A. CD4<sup>+</sup> T cells and CD40 ligand (16%)
- B. CD8<sup>+</sup> T cells and perforins (16%)
- C. Dendritic cells and MHC II (21%)
- D. Macrophages and IL-6 (39%)
- E. Plasma cells and IgM (6%)

Omitted

Correct answer

D



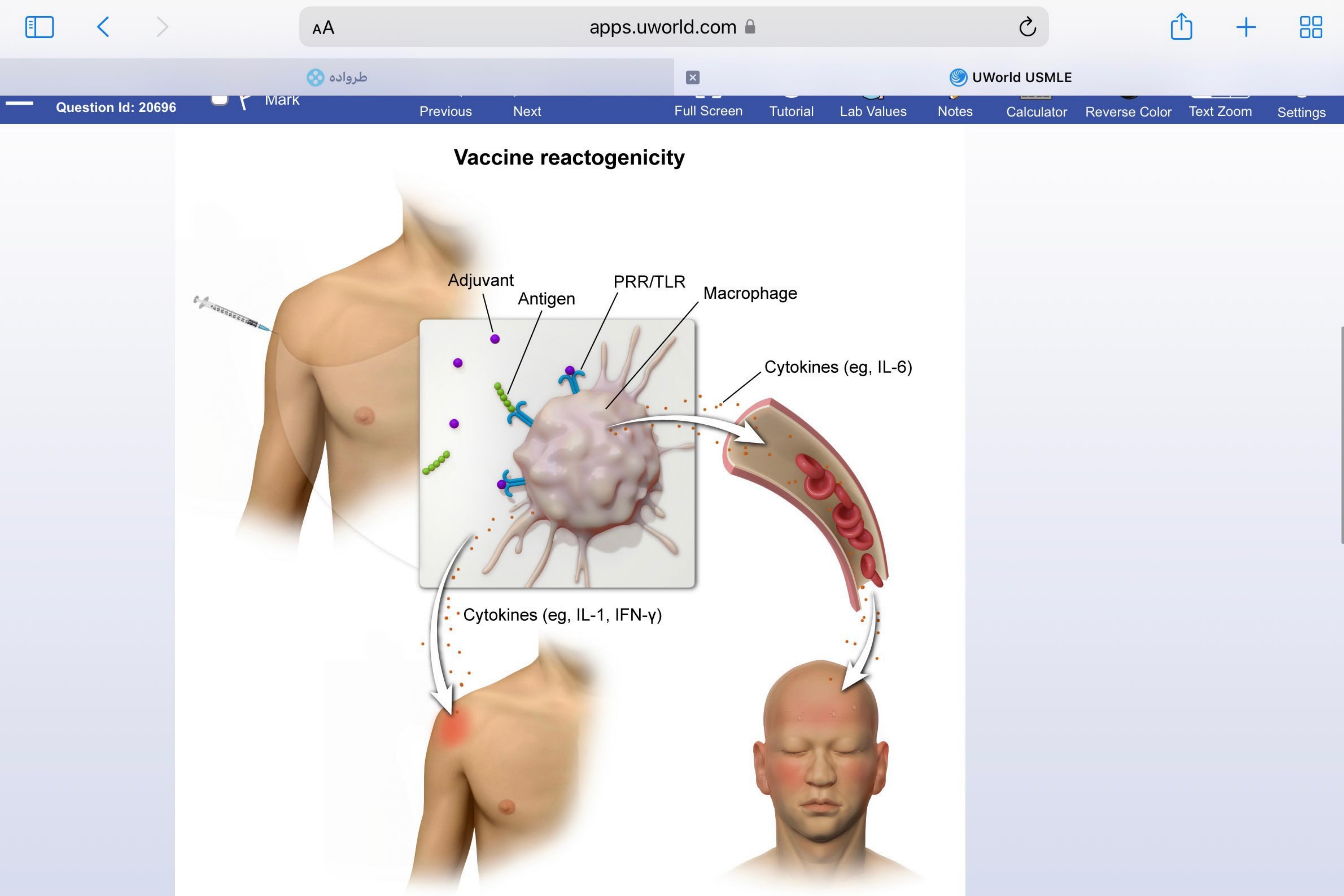
39%

Answered correctly

02 secs  
Time Spent2023  
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## Explanation

Vaccine reactogenicity



The screenshot shows a mobile application interface for UWorld USMLE. At the top, there are navigation icons for back, forward, and search, along with a zoom icon labeled 'AA' and a URL bar 'apps.uworld.com'. The main content area displays a photograph of a young boy's torso. Two labels are overlaid on the image: 'Local inflammation' pointing to the left side of his chest and 'Fever' pointing to his forehead. Below the image, the text 'PRR/TLR = Pattern recognition receptor/toll-like receptor.' is displayed. The bottom of the screen features a blue navigation bar with various icons and text labels: 'Question Id: 20696', 'Mark', 'Previous', 'Next', 'Full Screen', 'Tutorial', 'Lab Values', 'Notes', 'Calculator', 'Reverse Color', 'Text Zoom', and 'Settings'.

This boy developed fever, irritability, and local inflammatory symptoms (eg, redness, tenderness, swelling) within hours of vaccination, indicating **reactogenicity**, an inflammatory reaction that occurs shortly after vaccination.

Vaccinations typically inject a foreign, unencountered antigen into subcutaneous tissue in order to promote the development of adaptive immunity against the antigen. However, foreign antigens can also trigger a **rapid-onset innate immune response** driven by the presence of **pattern recognition receptors** (eg, toll-like receptors) on local stromal and local/circulating immune cells (eg, **macrophages**, monocytes, mast cells).

Pattern recognition receptors identify conserved motifs present on many pathogens (eg, lipopolysaccharide). Activation of these receptors leads to the release of **pyrogenic cytokines** (eg, TNF-alpha, IL-1, **IL-6**), which can cause **local inflammation** (eg, edema, warmth, swelling) due to increased vascular permeability/immune cell recruitment and **systemic inflammation** (eg, fever, irritability, fatigue, headache) due to increased circulating inflammatory cytokines.

Many vaccines also contain **adjuvants** (eg, aluminum salts, virosomes, oil-in-water) to increase the immune response to the injected antigen. Adjuvants are strongly immunostimulatory and frequently increase the risk of reactogenicity. However, manifestations of reactogenicity tend to improve 24-36 hours after vaccination.

**(Choices A and C)** Dendritic cells are antigen-presenting cells (APCs) that display foreign antigens on their surface on major histocompatibility complex class II molecules. CD4 T lymphocytes with antigen-specific receptors bind to the antigen on the APCs and are costimulated by the interaction between CD80/86 on the APCs and CD28 on the T-cell surface. Activated CD4 T-cells then increase display of **CD40 ligand**, which binds



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cause local inflammation (eg, edema, warmth, swelling) due to increased vascular permeability, immune cell recruitment and **systemic inflammation** (eg, fever, irritability, fatigue, headache) due to increased circulating inflammatory cytokines.

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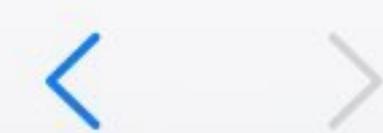
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**(Choice B)** Cytotoxic T-cells recognize a foreign antigen on major histocompatibility complex class I and release perforins to induce cell lysis; they primarily attack cells infected by intracellular pathogens (eg, viruses). Cytotoxic T-cells do not significantly contribute to vaccination reactions within hours of vaccination.

**(Choice E)** Some activated B-cells differentiate into short-lived plasma cells that secrete IgM. However, this typically takes several days to occur and would not cause local inflammatory symptoms.

#### Educational objective:

Vaccine reactogenicity is a local (eg, warmth, swelling, edema) and systemic (eg, fatigue, fever, headache) inflammatory reaction to the vaccine due to the innate immune response. It is primarily caused by pattern recognition receptors present on the surface of macrophages and mast cells, which identify the antigen and release inflammatory cytokines (eg, IL-1, IL-6).



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A 62-year-old man is found dead in his apartment. An autopsy shows diffuse cerebral edema, laryngeal edema, and hyperinflated lungs. Which of the following is the most likely cause of death in this patient?

- A. Acute myocardial infarction (2%)
- B. Anaphylaxis (68%)
- C. Chronic obstructive pulmonary disease exacerbation (23%)
- D. Meningococcal meningitis (2%)
- E. Seizures (3%)

Omitted

Correct answer

B



68%

Answered correctly



05 secs

Time Spent



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Version

### Explanation

This patient with diffuse cerebral edema, laryngeal edema, and hyperinflated lungs most likely died from anaphylaxis. **Anaphylaxis** classically involves a [type 1 \(immediate\) hypersensitivity](#) reaction to an antigen that leads to **IgE-mediated mast cell and basophil degranulation**. The resulting sudden and massive release of inflammatory mediators (eg, histamine, leukotrienes) into the circulation can quickly lead to **airway obstruction** (eg, bronchospasm, oropharyngeal edema) and **distributive shock** (ie, profound peripheral vasodilation).

Although some patients (eg, those who experience rapid cardiovascular collapse) have no significant gross autopsy findings, the most common abnormal findings resulting from anaphylaxis include the following:



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Although some patients (eg, those who experience rapid cardiovascular collapse) have no significant gross autopsy findings, the most common abnormal findings resulting from anaphylaxis include the following:

- **Laryngeal and/or pharyngeal edema**
- **Hyperinflation of the lungs** (due to air trapping from airway obstruction)
- Cerebral edema (due to cerebral hypoxia)

Cutaneous abnormalities (eg, urticaria, flushing) may also be present because anaphylaxis often involves the skin.

To help confirm the diagnosis, patient serum can be sent for tryptase level analysis. **Tryptase**, a mediator released from mast cells, is elevated in many cases of anaphylaxis.

**(Choice A)** In most cases of sudden death due to acute myocardial infarction (MI), death is due to an arrhythmia resulting from acute coronary occlusion, and an occlusive thrombus is often present on autopsy. Although cerebral edema could be present from hypoxia, an acute MI would not be expected to cause laryngeal edema and hyperinflated lungs.

**(Choice C)** Patients with sudden death from chronic obstructive pulmonary disease (COPD) exacerbation could have hyperinflation of the lungs due to airway obstruction, as well as cerebral edema due to hypoxia. However, because COPD is a disease of the lower airway, it would not be expected to cause upper airway (eg, laryngeal) edema.

**(Choice D)** Meningococcal meningitis can cause cerebral edema, as found on autopsy, but also commonly causes a purulent exudate in the meninges. It would not be expected to cause laryngeal edema or lung hyperinflation.

**(Choice E)** Sudden unexpected death in epilepsy is not well understood but is believed to be caused by central



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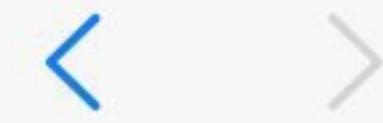
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**(Choice E)** Sudden unexpected death in epilepsy is not well understood but is believed to be caused by central apnea or cardiac arrhythmias. It is the most common seizure-related cause of death and is frequently associated with cerebral edema, which is demonstrated on autopsy. However, laryngeal edema and lung hyperinflation are not expected. In addition, tongue lacerations and cutaneous abrasions are frequently present.

### Educational objective:

Anaphylaxis (type 1 hypersensitivity) can quickly lead to respiratory compromise (eg, bronchospasm, oropharyngeal edema) and distributive shock. The most common autopsy findings include upper airway edema, hyperinflation of the lungs from airway obstruction, and cerebral edema from hypoxia.

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A 62-year-old man is found dead in his apartment. An autopsy shows diffuse cerebral edema, laryngeal edema, and hyper.

### Exhibit Display

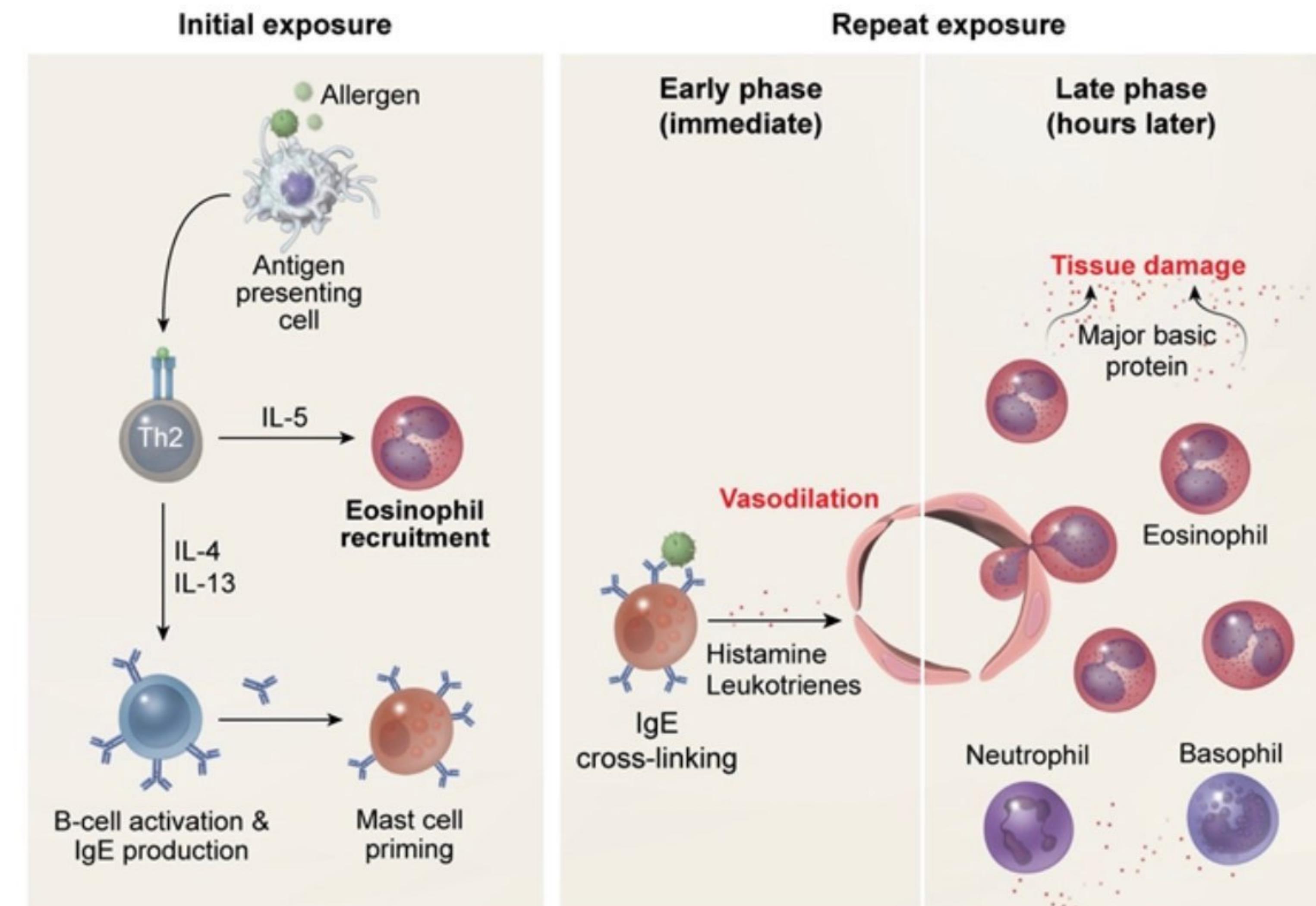
- A.
- B.
- C.
- D.
- E.

Omitted  
Correct ans:  
B

### Explanation

This patient  
anaphylaxis  
leads to Ig  
inflammato  
(eg, bronch)

#### Type 1 hypersensitivity reaction



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Zoom In

Zoom Out

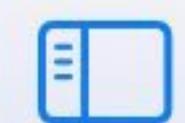
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Although some patients (eg, those who experience rapid cardiovascular collapse) have no significant gross autopsy findings, the most common abnormal findings resulting from anaphylaxis include the following:



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A 62-year-old woman undergoes hip replacement surgery. The patient has a history of advanced hip osteoarthritis that limits her daily activities. She has no other medical conditions and no known drug allergies. After appropriate preoperative evaluation, total hip arthroplasty is performed under general anesthesia. The intraoperative course is uncomplicated, and after recovery from anesthesia, patient-controlled intravenous morphine is started for pain control. Several minutes later, the patient reports generalized itching. Physical examination reveals hypotension, tachycardia, and mild bilateral wheezing but no rashes. Which of the following drug effects is most likely responsible for this patient's current condition?

- A. Decreased myocardial contractility (1%)
- B. Decreased sympathetic output (4%)
- C. Direct mast cell degranulation (72%)
- D. Formation of drug-IgE complexes (17%)
- E. Increased 5-lipoxygenase activity (4%)

Omitted

Correct answer

C



72%

Answered correctly



02 secs

Time Spent



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### Explanation

Opioids (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can





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**Opioids** (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity (eg, anaphylaxis). However, true IgE-mediated allergic reaction is rare with opioids (**Choice D**), and suggestive symptoms rarely indicate the need to avoid opioids altogether. Because direct mast cell degranulation tends to be most prominent with relatively low-potency opioids (eg, morphine, meperidine), a relatively high-potency opioid (eg, fentanyl) is usually better tolerated.

Other drugs that can have a similar **non-IgE-mediated effect** on mast cell degranulation include [vancomycin](#) and radioiodine contrast.

**(Choice A)** Halothane, an inhalation anesthetic, is rarely used but can cause hypotension via direct suppression of myocardial contractility. It is not associated with itching and wheezing.

**(Choice B)** Because pain increases sympathetic output, opioid analgesia can reduce sympathetic output and thus decrease heart rate and blood pressure. However, this does not explain the itching and wheezing.

**(Choice E)** Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase, which leads to [increased](#) 5-lipoxygenase activity. This effect can precipitate bronchoconstriction and wheezing due to increased production of leukotrienes (ie, NSAID-exacerbated respiratory disease); however, itching and hypotension are not expected.

#### Educational objective:

Opioids (eg, morphine) can generate a pseudoallergic response by directly activating mast cells to stimulate degranulation, releasing histamine and other vasoactive mediators. This nonimmunologic reaction can cause itching, urticarial rash, wheezing, hypotension, and tachycardia that closely mimic true IgE-mediated type 1 hypersensitivity. However, true IgE-mediated allergic reaction is rare with opioids.

D

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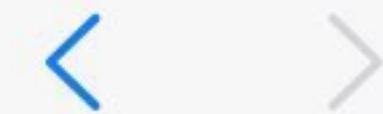
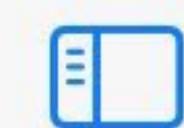
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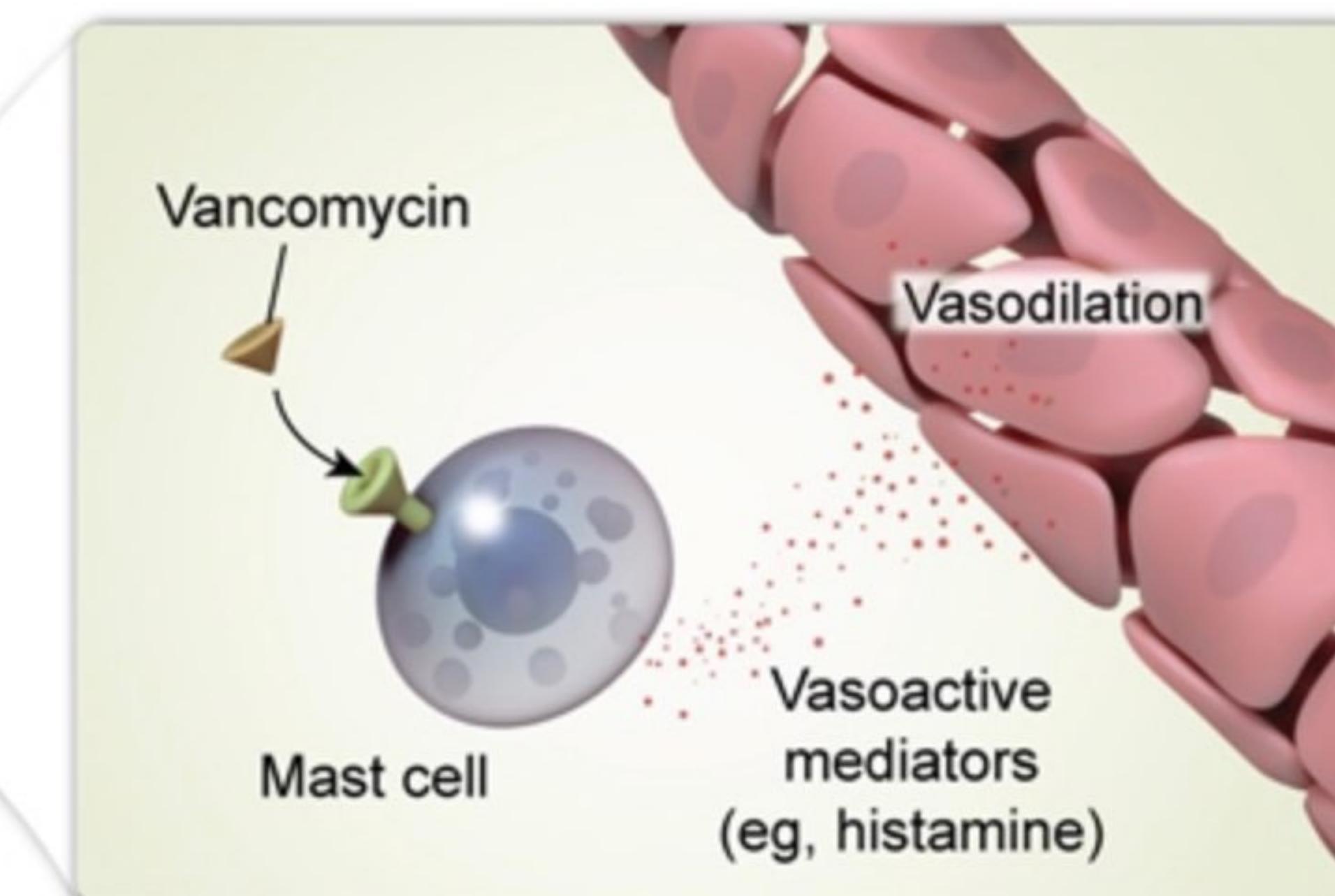
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Opioids (eg, morphine) can generate a **pseudoallergic** response by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic** reaction can cause itching, urticaria, and hypotension.

Exhibit Display



### Vancomycin infusion reaction



Direct mast cell activation (IgE independent)

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Zoom In

Zoom Out



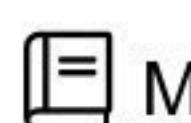
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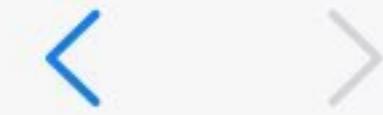
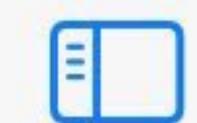


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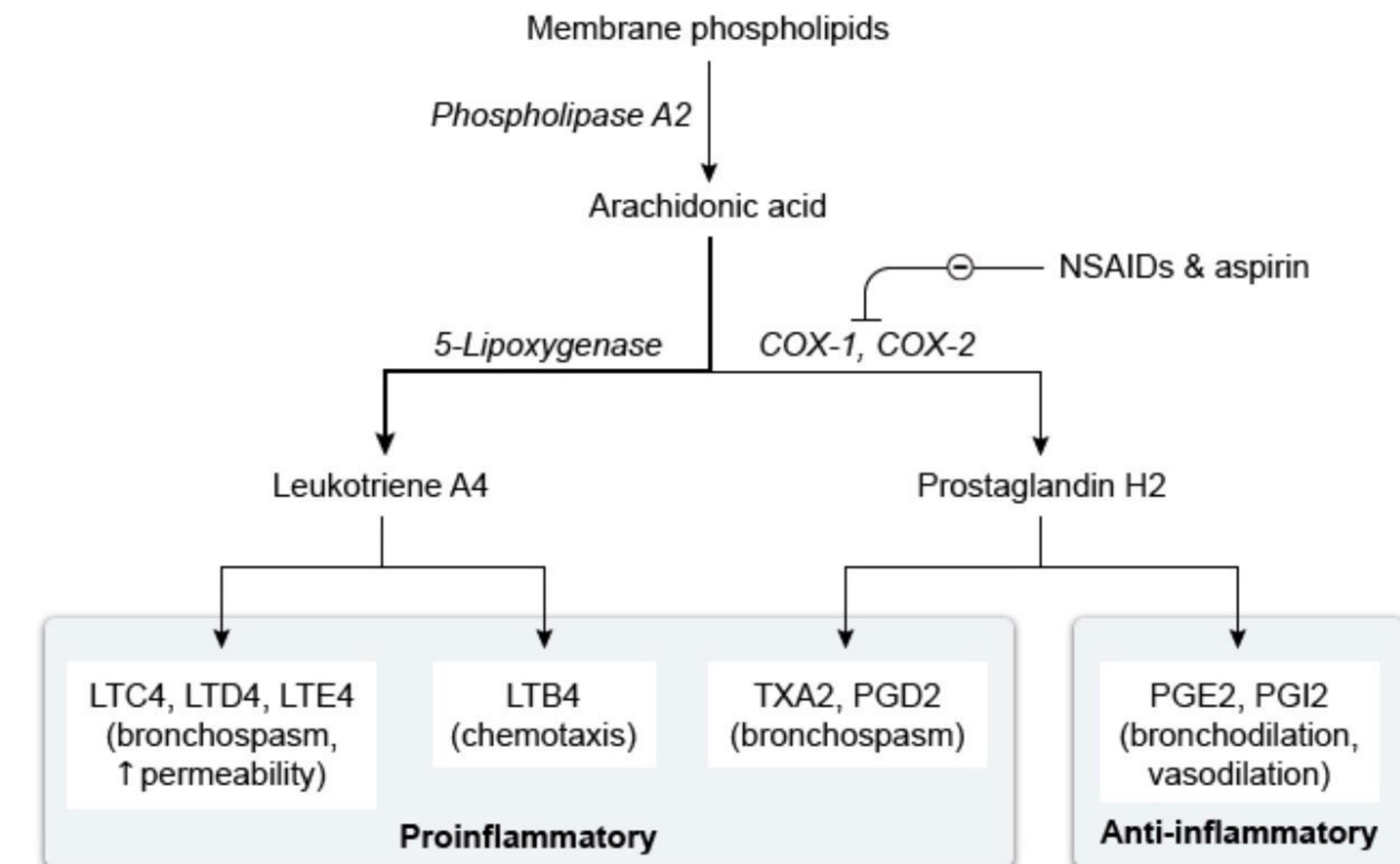
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Opioids (eg, morphine) can generate a **pseudoallergic response** by **directly stimulating mast cell degranulation**, releasing **histamine** and other vasoactive mediators. This **nonimmunologic reaction** can cause itching.

Exhibit Display



### Arachidonic acid pathway in NSAID-exacerbated respiratory disease



COX = cyclooxygenase; LT = leukotriene; NSAIDs = nonsteroidal anti-inflammatory drugs; PG = prostaglandin; TX = thromboxane.

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Zoom In



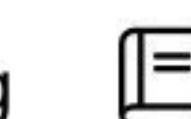
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Item 8 of 19 Question Id: 21470

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A 22-year-old woman comes to the emergency department after development of a diffuse pruritic rash following a meal at a buffet restaurant an hour ago. She also felt light-headed and nearly fainted. The patient has no prior medical conditions and takes no medications. Temperature is 37 C (98.6 F), blood pressure is 96/52 mm Hg, pulse is 126/min, and respirations are 16/min. Physical examination shows mild lip swelling; the tongue appears normal. Heart auscultation demonstrates regular tachycardia without extraneous sounds. Lung sounds are clear with normal work of breathing. Skin examination shows confluent urticaria on the neck, shoulders, and abdomen. Intravenous fluids are begun, and intramuscular epinephrine is administered immediately. In addition to its effect on airway and circulation, this medication is most likely to improve this patient's condition through which of the following mechanisms?

- A. Blockade of tissue histamine receptors (25%)
- B. Decreased IgE Fc receptors on mast cells (5%)
- C. Decreased leukotriene synthesis in leukocytes (13%)
- D. Decreased mediator release from mast cells (42%)
- E. Decreased number of circulating eosinophils (13%)

Omitted  
Correct answer  
D

42%  
Answered correctly

01 sec  
Time Spent

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Version

### Explanation

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Anaphylaxis	
<b>Triggers</b>	<ul style="list-style-type: none"><li>• Immune mediated (eg, medications, food, insect stings)</li><li>• Nonimmune mediated (eg, intravenous contrast, mast cell activation syndrome)</li></ul>
<b>Clinical manifestations</b>	<ul style="list-style-type: none"><li>• Cardiovascular<ul style="list-style-type: none"><li>◦ Vasodilation → hypotension &amp; tissue edema</li><li>◦ Tachycardia</li></ul></li><li>• Respiratory<ul style="list-style-type: none"><li>◦ Upper airway edema → stridor &amp; hoarseness</li><li>◦ Bronchospasm → wheezing</li></ul></li><li>• Cutaneous<ul style="list-style-type: none"><li>◦ Urticarial rash, pruritus, flushing</li></ul></li><li>• Gastrointestinal<ul style="list-style-type: none"><li>◦ Nausea, vomiting, abdominal pain</li></ul></li></ul>
<b>Treatment</b>	<ul style="list-style-type: none"><li>• Intramuscular epinephrine</li></ul>

This patient with sudden-onset rash and hypotension after ingesting a likely allergen has **anaphylaxis**.

Anaphylaxis classically involves a [type 1 \(immediate\) hypersensitivity](#) reaction to an antigen, resulting in IgE-mediated mast cell and basophil degranulation. Sudden and **massive release of inflammatory mediators** (eg, histamine, leukotrienes) into the circulation can quickly lead to urticaria, oropharyngeal edema (eg, lip swelling), and shock (eg, hypotension, tachycardia).

**Epinephrine** is the only pharmacologic therapy that both decreases the release of inflammatory mediators from

**Epinephrine** is the only pharmacologic therapy that both decreases the release of inflammatory mediators from mast cells and addresses all other manifestations of anaphylaxis. It binds to adrenergic receptors (eg, beta-2 receptors) on the surface of mast cells, **inhibiting mast cell degranulation**. In addition, it **counteracts existing inflammatory effects** via widespread stimulation of alpha- and beta-adrenergic receptors:

- Alpha-1: causes vasoconstriction and decreases vascular permeability, raising blood pressure and decreasing upper airway edema
- Beta-1: increases cardiac contractility and cardiac output, improving blood pressure and peripheral perfusion
- Beta-2: causes bronchodilation, relieving airflow obstruction

Because of its ability to both treat and prevent further inflammatory mediator effects, epinephrine is the first-line treatment for anaphylaxis.

**(Choice A)** H1 antagonists (eg, diphenhydramine) block tissue histamine receptors, preventing the effects of circulating histamine on capillaries (eg, vasodilation, increased vascular permeability). However, they do not decrease the mast cell release of histamine or other inflammatory mediators.

**(Choice B)** Omalizumab is a monoclonal anti-IgE antibody that binds to free IgE at the same site where IgE normally binds to mast cell IgE Fc receptors. It prevents receptor binding and decreases circulating IgE levels, which eventually induces IgE Fc receptor down-regulation to help stabilize mast cells.

**(Choice C)** Zileuton, a medication commonly used in the management of asthma, decreases the leukocyte synthesis of leukotrienes by **inhibiting 5-lipoxygenase**. This results in decreased leukotriene activity, reducing inflammation and bronchospasm.

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## perfusion

- Beta-2: causes bronchodilation, relieving airflow obstruction

Because of its ability to both treat and prevent further inflammatory mediator effects, epinephrine is the first-line treatment for anaphylaxis.

**(Choice A)** H1 antagonists (eg, diphenhydramine) block tissue histamine receptors, preventing the effects of circulating histamine on capillaries (eg, vasodilation, increased vascular permeability). However, they do not decrease the mast cell release of histamine or other inflammatory mediators.

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**(Choice C)** Zileuton, a medication commonly used in the management of asthma, decreases the leukocyte synthesis of leukotrienes by [inhibiting 5-lipoxygenase](#). This results in decreased leukotriene activity, reducing inflammation and bronchospasm.

**(Choice E)** Glucocorticoids reduce inflammation by several mechanisms. One such mechanism is by promoting eosinophil apoptosis, either directly or by decreasing production of IL-5, which usually promotes eosinophil survival. This decreases the number of circulating eosinophils.

### Educational objective:

Anaphylaxis is a type 1 (immediate) hypersensitivity reaction involving IgE-mediated mast cell and basophil degranulation. Epinephrine is the primary treatment for anaphylaxis because it decreases further mast cell release of inflammatory mediators and counteracts existing systemic inflammatory effects (eg, shock, bronchoconstriction).

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manifestations

bronchospasm → wheezing

Exhibit Display

Type 1 hypersensitivity reaction

Initial exposure

Allergen

Antigen presenting cell

Th2

IL-5

Eosinophil recruitment

IL-4 IL-13

B-cell activation & IgE production

Mast cell priming

Repeat exposure

Early phase (immediate)

IgE cross-linking

Histamine Leukotrienes

Vasodilation

Late phase (hours later)

Tissue damage

Major basic protein

Eosinophil

Neutrophil

Basophil

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The diagram illustrates the Type 1 hypersensitivity reaction in two phases: Initial exposure and Repeat exposure.

**Initial exposure:** An allergen is taken up by an antigen-presenting cell (APC). The APC presents the allergen to a Th2 lymphocyte. The Th2 cell secretes IL-5, which promotes eosinophil recruitment. It also secretes IL-4 and IL-13, which stimulate B-cell activation and IgE production. Simultaneously, the APC presents the allergen to a mast cell, leading to its priming.

**Repeat exposure:** In the early phase (immediate), IgE antibodies on the mast cell surface cross-link upon re-exposure to the allergen. This triggers the release of histamine and leukotrienes, leading to vasodilation. In the late phase (hours later), eosinophils, neutrophils, and basophils are recruited to the site of tissue damage, where they release major basic protein, causing further inflammation and tissue damage.

This patient  
Anaphylaxis  
mediated r  
histamine,  
and shock

Epinephrine  
mast cells  
receptors)  
inflammation

- Alpha-1: decreases perfusion
- Beta-1: increases perfusion

- Beta-2: causes bronchodilation, relieving airflow obstruction

Because of its ability to both treat and prevent further inflammatory mediator effects, epinephrine is the first-line

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mast cells and addresses all other manifestations of anaphylaxis. It binds to adrenergic receptors (eg, beta-2 receptors) inflammatory

Exhibit Display

Mast cells & allergic response

The diagram illustrates the biology of a mast cell and its interaction with a target cell. An antigen triggers the release of IgE from a浆细胞. IgE binds to the FCεR1 receptor on the mast cell membrane. This triggers gene transcription and phospholipase A2 activity. Phospholipase A2 releases arachidonic acid from the lipid bilayer. Arachidonic acid is converted into leukotrienes by the enzyme 5-lipoxygenase. Leukotrienes bind to the CysLT1 receptor on a nearby target cell. Histamine is also released from preformed vesicles and binds to the H1 receptor on the target cell. Cromoglycates inhibit the release of histamine and leukotrienes. Omalizumab (anti-IgE antibody) prevents IgE from binding to the mast cell. Glucocorticoids inhibit gene transcription. Montelukast and Zafirlukast inhibit the CysLT1 receptor. Zileuton inhibits 5-lipoxygenase.

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**(Choice A**  
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**(Choice E)** Glucocorticoids reduce inflammation by several mechanisms. One such mechanism is by promoting eosinophil apoptosis, either directly or by decreasing production of IL-5, which usually promotes eosinophil

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Question Id: 21470

perfusion

- Beta-2 Exhibit Display

Because of treatment for

**(Choice A)** circulating decrease t

**(Choice B)** normally b which ever

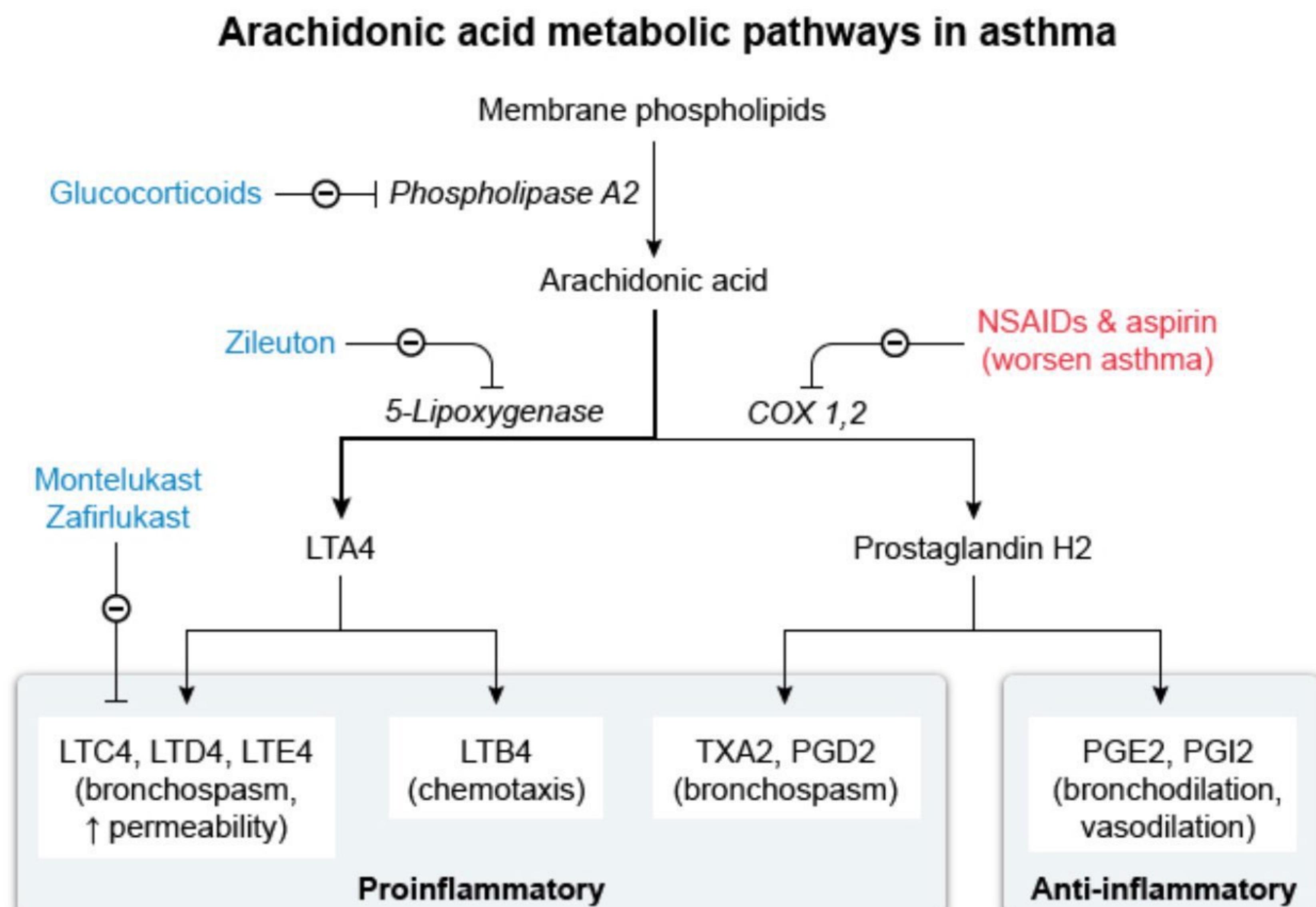
**(Choice C)** synthesis of inflammatory

**(Choice E)** eosinophil survival. T

**Education**

Anaphylaxis degranulation

release of inflammatory mediators and counteracts existing systemic inflammatory effects (eg, shock, bronchoconstriction).



LT = leukotriene; NSAIDs = nonsteroidal anti-inflammatory drugs;  
PG = prostaglandin; TX = thromboxane.

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Item 9 of 19

Question Id: 556



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A 5-year-old child is brought to the emergency department by his parents for right arm pain. The patient reports that he was playing hide and seek outside and felt a sharp pain on his arm while hiding in some thick bushes. His parents suspect that something had stung him. Physical examination shows an edematous and erythematous plaque with mild central pallor. A residual stinger, located central to the lesion, is readily extracted. The physical examination is otherwise not significant. Which of the following substances is most likely directly responsible for the skin findings observed in this patient?

- A. C3b (2%)
- B. IL-2 (4%)
- C. Histamine (86%)
- D. Lysozyme (1%)
- E. TNF- $\alpha$  (5%)

Omitted

Correct answer

C



86%

Answered correctly



02 secs

Time Spent



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### Explanation

This child is experiencing a local allergic reaction ([type I hypersensitivity](#)) to an insect sting. The cutaneous findings are consistent with [a wheal-and-flare reaction](#), an erythematous papule or plaque often with central pallor (wheal) and peripheral erythema (flare).

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During initial allergen exposure, a patient predisposed to an allergic response will undergo antibody class switching from IgM to **IgE antibodies** specific for the allergen. IgE produced by B lymphocytes and plasma cells then binds to high-affinity IgE Fc receptors on **basophils and mast cells**. Re-exposure to the allergen results in cross-linking of bound IgE antibodies with subsequent degranulation and release of inflammatory mediators (eg, **histamine**, proteases [tryptase], leukotrienes, prostaglandins). Localized vasodilation and increased vascular permeability result in the characteristic wheal-and-flare lesions. In severe cases, widespread release of these agents can also cause systemic vasodilation, bronchoconstriction, and massive fluid shifts, leading to anaphylactic shock and potentially death.

**(Choice A)** C3b, the larger subunit produced by cleavage of complement component 3, binds to pathogens and enhances phagocytosis. The C3b component of immune complexes formed by type III hypersensitivity reactions can also bind to CR1 receptors on erythrocytes, facilitating their clearance in the liver and spleen.

**(Choice B)** IL-2 is a cytokine produced by T<sub>H</sub>1 lymphocytes that increases proliferation and activity of helper, cytotoxic, and regulatory T cells as well as NK cells. T<sub>H</sub>1 cells are responsible for inducing macrophage and cytotoxic T lymphocyte-mediated (type IV) inflammatory reactions. In contrast, IL-4 is responsible for driving the production of T<sub>H</sub>2 cells, which promote antibody-mediated (humoral) immunity and facilitate type I hypersensitivity.

**(Choice D)** Lysozyme is an antimicrobial enzyme found in specific granules of neutrophils and bodily secretions (tears, mucus). Lysozyme functions by hydrolyzing bonds within the peptidoglycan cell walls of bacterial organisms. It is an important component of innate immunity, not hypersensitivity reactions.

**(Choice E)** TNF- $\alpha$  is a proinflammatory cytokine produced by macrophages and T cells that induces and maintains granuloma formation (important for host defense against tuberculosis). It also plays a pathogenic role in inflammatory conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. TNF- $\alpha$  may

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**(Choice A)** C3b, the larger subunit produced by cleavage of complement component 3, binds to pathogens and enhances phagocytosis. The C3b component of immune complexes formed by type III hypersensitivity reactions can also bind to CR1 receptors on erythrocytes, facilitating their clearance in the liver and spleen.

**(Choice B)** IL-2 is a cytokine produced by T<sub>H</sub>1 lymphocytes that increases proliferation and activity of helper, cytotoxic, and regulatory T cells as well as NK cells. T<sub>H</sub>1 cells are responsible for inducing macrophage and cytotoxic T lymphocyte-mediated (type IV) inflammatory reactions. In contrast, IL-4 is responsible for driving the production of T<sub>H</sub>2 cells, which promote antibody-mediated (humoral) immunity and facilitate type I hypersensitivity.

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**(Choice E)** TNF- $\alpha$  is a proinflammatory cytokine produced by macrophages and T cells that induces and maintains granuloma formation (important for host defense against tuberculosis). It also plays a pathogenic role in inflammatory conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. TNF- $\alpha$  may be elevated in type IV (delayed type) hypersensitivity, but not type I.

#### Educational objective:

Wheal-and-flare lesions usually result from allergic (type I hypersensitivity) reactions. On initial exposure, an allergen (eg, insect venom) promotes antibody class switching to IgE. Subsequent exposure promotes cross-linking of IgE on basophils and mast cells, resulting in degranulation and release of multiple vasoactive mediators, including histamine.

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C. Histamine (86%)

D.

E.

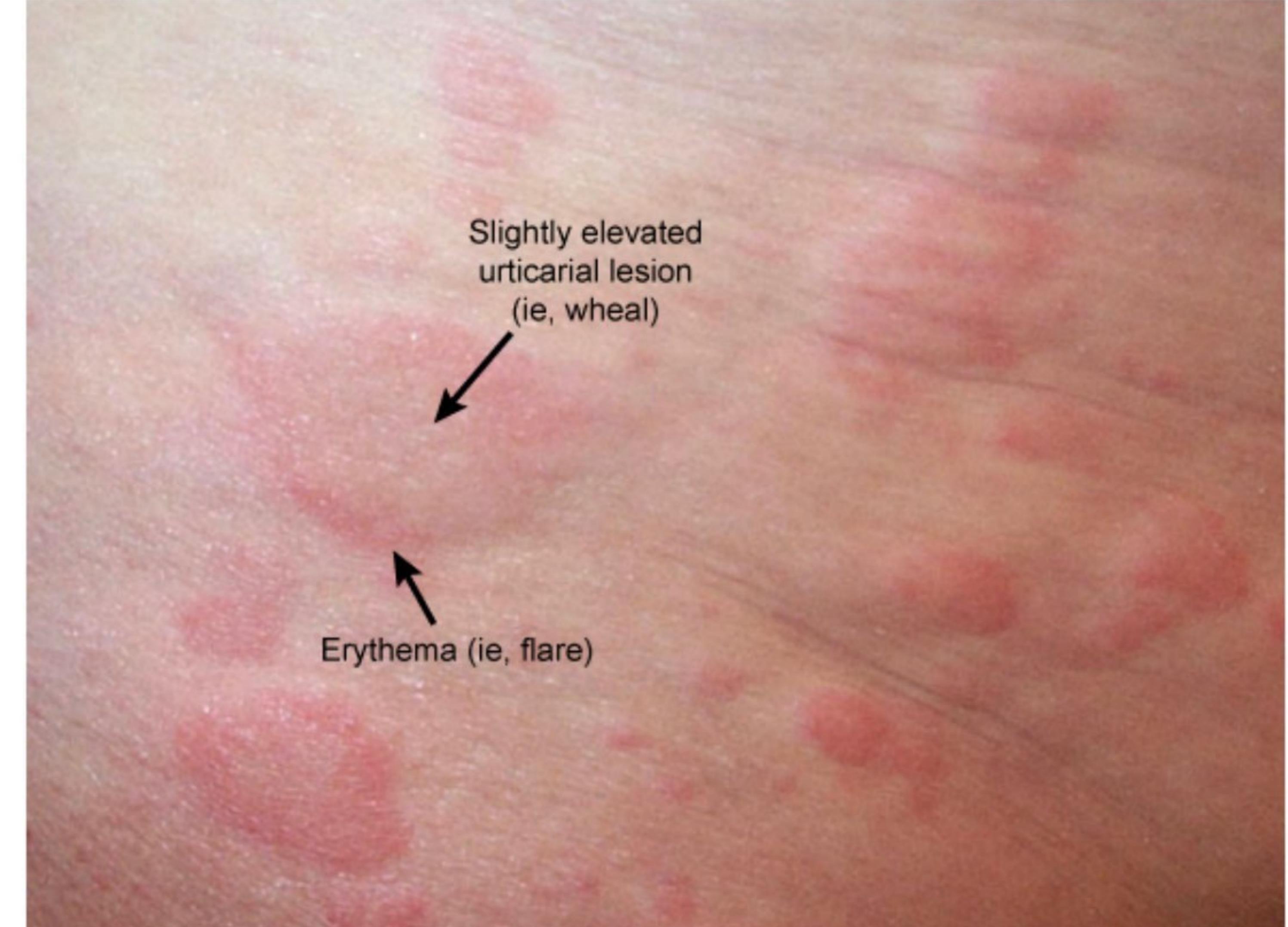
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Exhibit Display

**Wheal and flare**



Slightly elevated urticarial lesion (ie, wheal)

Erythema (ie, flare)

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**(Choice A)** C3b, the larger subunit produced by cleavage of complement component 3, binds to pathogens and enhances phagocytosis. The C3b component of immune complexes formed by type III hypersensitivity reactions

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Item 10 of 19 Question Id: 174

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A 75-year-old man comes to the urgent care center with acute onset of a pruritic rash after eating strawberries. The patient has no associated swelling in or around the mouth, no wheezing, and no difficulty breathing. Past medical history is notable for coronary artery disease, for which he takes atorvastatin, lisinopril, aspirin, and metoprolol. He also has a history of allergy to dog and cat dander. The patient does not use alcohol or tobacco. His family reports that he lives alone and his functional status has been declining. He walks with a cane, has poor vision, and is frequently forgetful. The patient also has occasional dizziness when standing up and a history of frequent falls. Which of the following would be the most appropriate medication to treat this patient's acute symptoms?

- A. Chlorpheniramine (6%)
- B. Diphenhydramine (15%)
- C. Hydroxyzine (5%)
- D. Loratadine (66%)
- E. Promethazine (5%)

Omitted  
Correct answer  
D

66%  
Answered correctly

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Time Spent

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### Explanation

This patient, with an acute, pruritic rash and history of environmental allergies, has a typical presentation of

The screenshot shows a mobile application interface for a medical question. At the top, there is a navigation bar with icons for back, forward, and search. The URL 'apps.uworld.com' is displayed in the address bar. Below the address bar is a toolbar with various icons: 'Item 10 of 19', 'Question Id: 174', 'Mark' (with a red flag icon), 'Previous' and 'Next' arrows, 'Full Screen', 'Tutorial', 'Lab Values', 'Notes' (with a pencil icon), 'Calculator' (with a '0.25' icon), 'Reverse Color' (with a black circle icon), 'Text Zoom' (with a 'A A A' icon), and 'Settings' (with a gear icon). The main content area contains text about urticaria (hives) and its treatment with antihistamines.

This patient, with an acute, pruritic rash and history of environmental allergies, has a typical presentation of urticaria (hives). Hives are triggered in most cases by IgE-dependent mast cell degranulation. As histamine is one of the primary mediators in this type of allergic reaction, **antihistamines** (ie, H1 histamine receptor antagonists) are the preferred treatment in most cases.

The side effects of antihistamines are largely due to blockade of other pathways, especially:

- **Cholinergic/muscarinic** (blurry vision, exacerbation of glaucoma, urine retention, delirium, constipation)
- **Alpha-adrenergic** (postural dizziness, falls)
- **Serotonergic** (appetite stimulation, weight gain)

These side effects are especially prominent with first-generation antihistamines (eg, hydroxyzine, promethazine, chlorpheniramine, diphenhydramine) (**Choices A, B, C and E**). Furthermore, first-generation antihistamines are lipophilic and easily cross the blood-brain barrier, where they may cause significant sedation and cognitive dysfunction. First-generation antihistamines are considered potentially inappropriate medications for **elderly patients**, especially those with pre-existing cognitive or functional impairment.

Newer-generation antihistamines (eg, loratadine, cetirizine) do not have the same degree of antimuscarinic, antiserotonergic, or anti-alpha adrenergic properties and their side effects are minimal. Moreover, second-generation antihistamines are less lipophilic, do not readily cross the blood-brain barrier, and are usually nonsedating.

#### **Educational objective:**

First-generation antihistamines can cause significant side effects due to blockade of cholinergic, alpha-adrenergic, and serotonergic pathways. They should be avoided in older patients with cognitive or functional impairments.

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Item 11 of 19 Question Id: 1612

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A 12-year-old girl is being evaluated for recurrent episodes of self-limited colicky abdominal pain and nausea lasting several days. She was also recently hospitalized for an episode of difficulty breathing. The patient has no significant past medical history, but her mother has a history of attacks of severe abdominal pain and diarrhea. Physical examination is unremarkable. Laboratory evaluation reveals decreased serum complement C4 and C1 esterase inhibitor levels. Which of the following drugs is contraindicated in this patient?

- A. Captopril (62%)
- B. Furosemide (4%)
- C. Methotrexate (19%)
- D. Metoprolol (4%)
- E. Penicillin (9%)

Omitted

Correct answer

A



62%

Answered correctly



02 secs

Time Spent



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## Explanation

C1 inhibitor



Kallikrein

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Item 11 of 19 Question Id: 1612

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graph TD; C1inhibitor_C1[C1 inhibitor] --> Kallikrein_Kallikrein[Kallikrein]; Kallikrein_Kallikrein --> Plasminogen_Plasminogen[Plasminogen]; Kallikrein_Kallikrein --> Kininogen_Kininogen[Kininogen]; Plasminogen_Plasminogen --> Plasmin_Plasmin[Plasmin]; Plasmin_Plasmin --> Fibrin_FibrinSplit[Fibrin → Fibrin split products]; Fibrin_FibrinSplit --> C1_C1[Activated C1]; C1_C1 --> C1inhibitor_C1; C1_C1 --> Angioedema_Angioedema[Angioedema]; Kininogen_Kininogen --> Bradykinin_Bradykinin[Bradykinin]; Bradykinin_Bradykinin -- ACE --> InactiveProducts_InactiveProducts[Inactive products];
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Low serum levels of C1 esterase inhibitor (and its substrate C4) are diagnostic of **hereditary angioedema**, an inherited autosomal dominant condition that causes episodes of painless, non-pitting, well-circumscribed edema. The face, neck, lips, and tongue are most commonly affected, but internal organs may also be involved. Angioedema affecting the tracheobronchial tree can cause respiratory obstruction and is potentially fatal.

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Question Id: 1612

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Low serum levels of C1 esterase inhibitor (and its substrate C4) are diagnostic of **hereditary angioedema**, an inherited autosomal dominant condition that causes episodes of painless, non-pitting, well-circumscribed edema. The face, neck, lips, and tongue are most commonly affected, but internal organs may also be involved. Angioedema affecting the tracheobronchial tree can cause respiratory obstruction and is potentially fatal. Angioedema of the gastrointestinal tract manifests with abdominal pain, vomiting, and diarrhea.

Normally, **C1 esterase inhibitor** suppresses activation of the C1 complement component and therefore the rest of the classic complement pathway. It also inactivates **kallikrein**, which catalyzes the conversion of kininogen to bradykinin. In **hereditary** angioedema, low C1 esterase inhibitor activity leads to an increase in active kallikrein and bradykinin levels. **Bradykinin** (along with C3a and C5a) mediate angioedema by increasing vasodilation and vascular permeability.

Angioedema may also occur as a side effect of **angiotensin-converting enzyme (ACE) inhibitor** medications. ACE normally catalyzes the conversion of angiotensin I into angiotensin II. ACE also converts bradykinin into inactive metabolites. ACE inhibitors can therefore lead to **bradykinin accumulation**. These medications should **not** be used in patients with hereditary angioedema as they may precipitate disease episodes.

**(Choice B)** Furosemide can cause hypokalemia, hyperuricemia, and hypovolemia. Ototoxicity may occur if furosemide is used with aminoglycosides.

**(Choice C)** Methotrexate can cause hepatitis, pulmonary fibrosis, and bone marrow suppression.

**(Choice D)** Metoprolol is a selective  $\beta_1$ -adrenergic blocker with few side effects. It may cause heart block in patients with conduction system disease and bronchoconstriction in asthmatic patients (rare due to  $\beta_1$  selectivity but can still occur).

**(Choice E)** The most common side effect of penicillin is hypersensitivity.