

Item 11 of 19
Question Id: 1612

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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 β_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 β_1 selectivity but can still occur).

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

Educational objective:

Angioedema can be hereditary (autosomal dominant) or acquired (associated with angiotensin-converting enzyme [ACE] inhibitor treatment). In hereditary angioedema, low C1 esterase inhibitor activity leads to increases in bradykinin activity. ACE inhibitors should not be used in these patients.

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A 25-year-old woman is brought to the emergency department 40 minutes after being stung by several wasps. She reports throat tightness and dizziness. She has no chronic medical conditions and takes no medication. Blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 32/min. Examination shows diffuse erythematous plaques over the trunk and 1+ pitting edema of the ankles. Which of the following is the most likely cause of this patient's hypotension?

- A. Chemical mediator-induced decreased myocardial contractility (1%)
- B. Chemical mediator-induced increased vascular permeability (85%)
- C. Impaired endogenous sympathetic nerve activity (1%)
- D. Toxin-mediated decreased myocardial contractility (0%)
- E. Toxin-mediated increased capillary permeability (10%)

Omitted

Correct answer

B



85%

Answered correctly



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Explanation

This patient with throat tightness, dizziness, hypotension, and urticaria (ie, diffuse erythematous plaques) has **anaphylaxis, a type I (immediate) hypersensitivity** reaction that occurs in response to an allergen (eg, wasp venom).

In patients who will eventually develop anaphylaxis, the **initial exposure** to an allergen results in antibody class

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In patients who will eventually develop anaphylaxis, the **initial exposure** to an allergen results in antibody class switching and the **production of allergen-specific IgE** by plasma cells. The allergen-specific IgE then **binds to an IgE receptor** on mast cells or basophils. **Subsequent reexposure** leads to allergen interaction with cell-bound IgE, IgE receptor aggregation, mast cell or basophil degranulation, and **release of chemical mediators** (histamine, prostaglandin, leukotrienes) that can cause anaphylactic shock.

Anaphylactic shock is characterized by profound **peripheral vasodilation**. Arteriolar vasodilation causes decreased systemic vascular resistance and consequent hypotension; venular vasodilation causes decreased central venous pressure and reduces venous return to the right atrium. In addition, the inflammatory chemical mediators **increase vascular permeability**, leading to large fluid shifts from the intravascular to the extravascular space; this **decreases intravascular volume** and worsens **hypotension**.

(Choice A) Chemical mediators (eg, histamine) released from cardiac mast cells may exert negative ionotropic effects on the heart, decreasing cardiac contractility. However, this is typically counterbalanced by the body's sympathetic response to anaphylaxis; increased sympathetic activity has a positive inotropic effect and increases the heart rate in an attempt to compensate for widespread peripheral vasodilation.

(Choice C) Increased, not impaired, endogenous sympathetic nerve activity is the body's early compensatory response in anaphylaxis. In response to anaphylaxis-induced hypotension, an intact **baroreceptor reflex** leads to increased sympathetic activity, tachycardia, and compensatory vasoconstriction.

(Choices D and E) A toxin-mediated decrease in myocardial contractility and an increase in capillary permeability occur in toxic shock syndrome (TSS). Most cases are linked to a prolonged use of tampons and wound/nasal packing (not wasp envenomation), which provide a medium for *Staphylococcus aureus* to replicate and release an exotoxin (eg, TSS toxin 1) that is capable of nonspecifically activating T cells (ie, a **superantigen**). The subsequent dramatic release of inflammatory cytokines results in increased capillary

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extravascular space; this **decreases intravascular volume** and worsens **hypotension**.

(Choice A) Chemical mediators (eg, histamine) released from cardiac mast cells may exert negative ionotropic effects on the heart, decreasing cardiac contractility. However, this is typically counterbalanced by the body's sympathetic response to anaphylaxis; increased sympathetic activity has a positive inotropic effect and increases the heart rate in an attempt to compensate for widespread peripheral vasodilation.

(Choice C) Increased, not impaired, endogenous sympathetic nerve activity is the body's early compensatory response in anaphylaxis. In response to anaphylaxis-induced hypotension, an intact [baroreceptor reflex](#) leads to increased sympathetic activity, tachycardia, and compensatory vasoconstriction.

(Choices D and E) A toxin-mediated decrease in myocardial contractility and an increase in capillary permeability occur in toxic shock syndrome (TSS). Most cases are linked to a prolonged use of tampons and wound/nasal packing (not wasp envenomation), which provide a medium for *Staphylococcus aureus* to replicate and release an exotoxin (eg, TSS toxin 1) that is capable of nonspecifically activating T cells (ie, a [superantigen](#)). The subsequent dramatic release of inflammatory cytokines results in increased capillary permeability and hypotension, as well as high fever and a diffuse, erythematous rash. In addition, the exotoxin can directly inhibit myocardial function.

Educational objective:

In anaphylaxis, allergen exposure triggers widespread IgE-mediated release of inflammatory chemical mediators (eg, histamine, prostaglandin, leukotrienes). These chemical mediators cause peripheral vasodilation and increase vascular permeability, leading to hypotension.

References

- [Regulation of vascular permeability in anaphylaxis.](#)

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Omitted Correct answer B

Explanations

This patient has a history of anaphylaxis to bee venom.

In patients with a history of anaphylaxis, switching a medication containing IgE to one that does not contain IgE, IgE receptors (histamine receptors) are activated.

Anaphylaxis is a severe, life-threatening allergic reaction that can lead to decreased blood pressure, central venous pressure, and mediators such as histamine and extravasation of fluid from blood vessels.

High-affinity IgE receptor activation

The diagram illustrates the process of mast cell degranulation. On the left, a mast cell is shown with several green Y-shaped IgE molecules bound to its surface. These IgE molecules are attached to specific receptors on the cell membrane. A multivalent antigen, represented by a cluster of red spheres, is also bound to the IgE molecules. An arrow points from this initial state to the right, where the mast cell is shown in a more rounded, swollen form. The green IgE molecules are now clustered together on the cell surface, a process labeled 'Receptor aggregation'. Small, granular vesicles are seen budding off from the cell surface and falling away, labeled 'Degranulation'.

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(Choice A)

effects on the heart, decreasing cardiac contractility. However, this is typically counterbalanced by the body's sympathetic response to anaphylaxis; increased sympathetic activity has a positive inotropic effect and increases

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Omitted Exhibit Display Correct ans: B

Explanation

This patient has anaphylaxis to bee venom.

In patients switching aeroallergens, an IgE receptor (histamine) on mast cells triggers a degranulation cascade, releasing mediators such as histamine and leukotrienes, which cause vasodilation and increased vascular permeability, leading to tissue damage.

Type 1 hypersensitivity reaction

Initial exposure:

- Allergen binds to Antigen presenting cell.
- Antigen presenting cell presents antigen to Th2 cell.
- Th2 cell secretes IL-5, leading to Eosinophil recruitment.
- Th2 cell secretes IL-4 and IL-13, leading to B-cell activation & IgE production.
- IgE binds to Mast cell priming.

Repeat exposure:

- Early phase (immediate): IgE cross-linking leads to Histamine Leukotrienes release, causing Vasodilation.
- Late phase (hours later): Major basic protein causes Tissue damage.
- Cells involved: Eosinophil, Neutrophil, Basophil.

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(Choice A) Chemical mediators (eg, histamine) released from cardiac mast cells may exert negative ionotropic effects on the heart, decreasing cardiac contractility. However, this is typically counterbalanced by the body's sympathetic response to anaphylaxis; increased sympathetic activity has a positive inotropic effect and increases

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mediators **increase vascular permeability**, leading to large fluid shifts from the intravascular to the extravascular space.

Exhibit Display

(Choice A)

effects on the sympathetic nervous system increase the heart rate.

(Choice C)

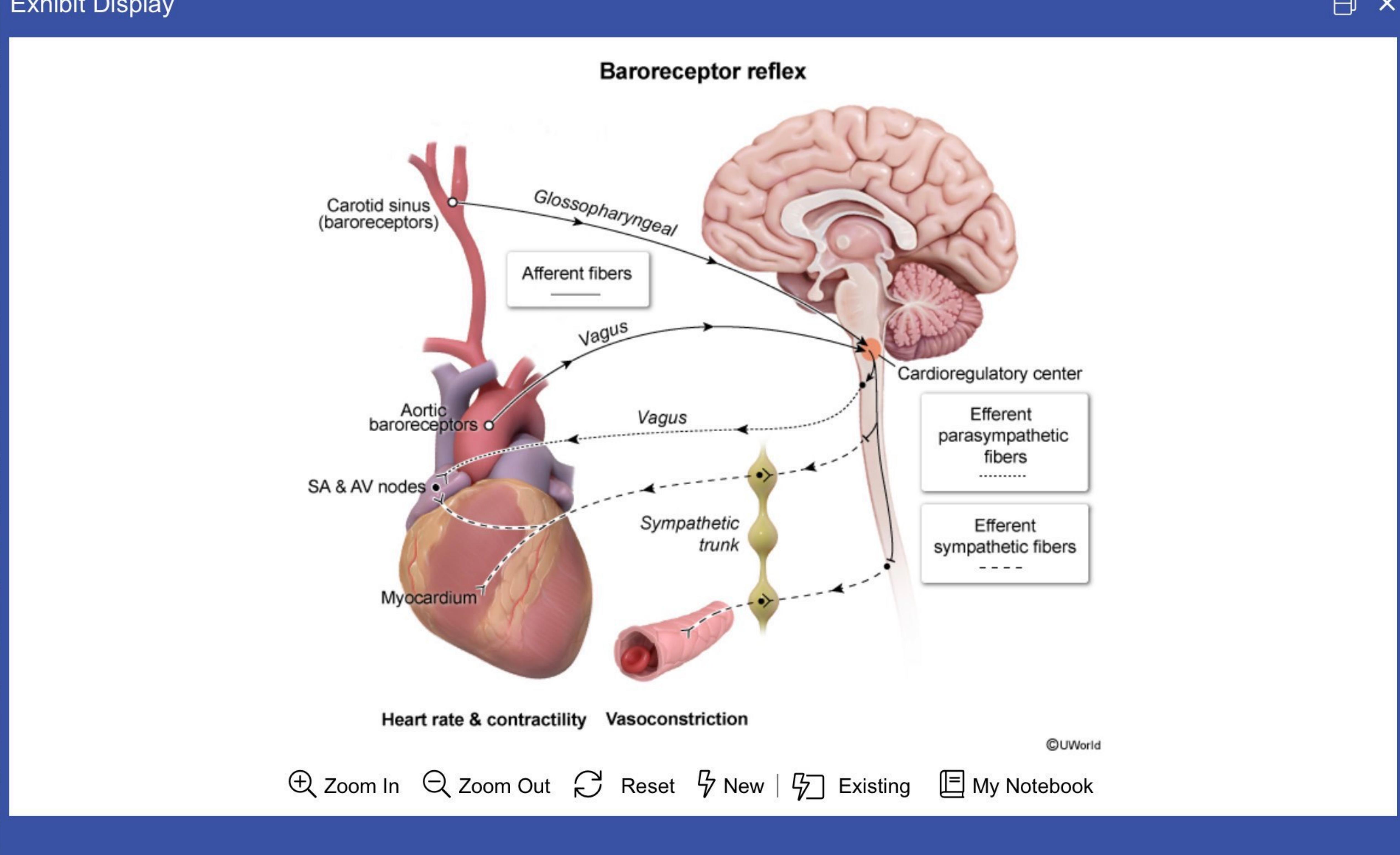
response is to increased blood volume.

(Choices D & E)

permeability at a wound/nasogastric tube site and release of superantigenic mediators increase vascular permeability and can directly affect the heart.

Education

In anaphylaxis (eg, histamine), mediators increase vascular permeability.



References

- Regulation of vascular permeability in anaphylaxis.

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A 56-year-old woman comes to the emergency department with facial swelling and difficulty breathing. She woke up today with a "feeling of fullness" in her lips, and 2 hours later her husband said that her lips looked puffy. There is no itching or skin rash. The patient has had no similar symptoms before. She has a history of gastroesophageal reflux disease and takes lansoprazole daily. She also began taking lisinopril 2 months ago for hypertension. The patient's blood pressure is 135/75 mm Hg. On examination, there is moderate swelling of her lips and tongue. Mild audible stridor without wheezing is present. Which of the following is the most likely mechanism responsible for this patient's symptoms?

- A. Bradykinin accumulation (61%)
- B. Hereditary C1-esterase inhibitor deficiency (22%)
- C. IgE-dependent mast cell degranulation (6%)
- D. Increased renin secretion (1%)
- E. Nonimmune mediated mast cell degranulation (7%)

Omitted
Correct answer
A

61%
Answered correctly

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Explanation

Causes of angioedema

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Causes of angioedema		
Mast cell activation	<ul style="list-style-type: none">Type 1 hypersensitivity reactions (IgE-mediated)Direct mast cell activation (eg, opioids)	Associated pruritus & urticaria
Excess bradykinin	<ul style="list-style-type: none">ACE inhibitorsC1 inhibitor deficiency (hereditary/acquired)	No pruritus or urticaria

Angioedema is a rare and potentially serious adverse effect of **ACE inhibitor therapy**. Symptoms typically appear within days of initiation but can also occur after weeks to years of therapy. Although **angioedema** can affect any tissue, it most commonly involves the tongue, lips, or eyelids. Laryngeal edema and difficulty breathing may also occur.

ACE inhibitor-induced angioedema is due to bradykinin accumulation. Normally, ACE is responsible for bradykinin breakdown. ACE inhibitors prevent bradykinin degradation, leading to increased levels. Bradykinin is a potent **vasodilator** that ultimately increases **vascular permeability**, causing significant angioedema. ACE inhibitors should be **discontinued** in patients who develop angioedema.

(Choice B) Hereditary C1-esterase inhibitor deficiency also causes bradykinin-mediated angioedema, but it usually presents in childhood and early adolescence. This patient's age and history make ACE inhibitor-induced bradykinin accumulation more likely.

(Choice C) Even though IgE-dependent mast cell degranulation can cause angioedema, it is more commonly associated with urticaria and pruritus. True hypersensitivity or an allergy to ACE inhibitors is very rare and not likely in this patient.

(Choice D) ACE inhibitors decrease production of angiotensin II, which reduces negative feedback on the renin-

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(Choice C) Even though IgE-dependent mast cell degranulation can cause angioedema, it is more commonly associated with urticaria and pruritus. True hypersensitivity or an allergy to ACE inhibitors is very rare and not likely in this patient.

(Choice D) ACE inhibitors decrease production of angiotensin II, which reduces negative feedback on the renin-angiotensin-aldosterone system, thereby promoting renin release. Increased renin levels are a natural compensatory response to ACE inhibitor therapy and have no role in causing angioedema.

(Choice E) In nonimmune mediated mast cell degranulation, there is direct activation of mast cells independent of IgE cross-linking. These pseudoallergic reactions can be caused by chemicals, heat, and certain drugs (eg, opiates, vancomycin) and are clinically similar to hypersensitivity and allergic reactions.

Educational objective:

Angioedema is a rare and serious adverse effect of ACE inhibitor therapy. ACE inhibition increases bradykinin levels, which increase vascular permeability and lead to angioedema. Symptoms include tongue, lips, or eyelid swelling and, less frequently, laryngeal edema and difficulty breathing. ACE inhibitors should be discontinued in affected patients.

References

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Omitted

Correct answer: A

61% Answered incorrectly

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Angioedema



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(Choice B)

usually presents in childhood and early adolescence. This patient's age and history make ACE inhibitor-induced bradykinin accumulation more likely.

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An 8-year-old girl is brought to the emergency department due to "not feeling well." The patient was at an outdoor picnic and began experiencing nausea, vomiting, abdominal cramps, and watery diarrhea 30 minutes ago. She also reports feeling dizzy. The patient has no prior medical conditions and takes no medications. Temperature is 37 C (98.6 F), blood pressure is 60/30 mm Hg, pulse is 140/min, and respirations are 28/min. On physical examination, the patient appears pale and listless. There is faint bilateral wheezing. The abdomen is soft and nontender. Scattered wheals are present. Which of the following is most responsible for this patient's current condition?

- A. Gram-negative bacterial endotoxin (8%)
- B. Gram-positive bacterial exotoxin (28%)
- C. Kallikrein-generated bradykinin (2%)
- D. Mast cell-derived histamine (58%)
- E. Vasoactive intestinal peptide (2%)

Omitted
Correct answer
D

58%
Answered correctly

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Explanation

Clinical features of anaphylaxis

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Clinical features of anaphylaxis	
Cutaneous/ mucosal	<ul style="list-style-type: none">Ocular: periorbital swelling, injected conjunctiva, tearingOral mucosa: swelling, tingling, or itching of tongue & lips; metallic tasteSkin: urticaria, flushing, pruritus
Respiratory	<ul style="list-style-type: none">Nose: congestion, rhinorrheaUpper airway: edema → hoarseness & stridorLower airway: bronchospasm → wheezing, dyspnea, tachypnea
Cardiovascular	<ul style="list-style-type: none">Vasodilation → hypotension, light-headedness/syncope, tachycardiaCardiac dysfunction, cardiac arrest
Gastrointestinal	<ul style="list-style-type: none">Nausea, vomiting, abdominal pain, diarrhea
Neurologic	<ul style="list-style-type: none">Headache, confusion, anxiety, feeling of impending doom

This patient's sudden-onset gastrointestinal symptoms, hypotension and tachycardia, wheezing, and urticaria (eg, wheals) are consistent with **anaphylaxis**. While at a picnic outdoors, this patient was likely exposed to an **allergen** (eg, insect sting) that caused **cross-linking** of basophil-bound and **mast cell–bound IgE antibodies**, inducing cellular activation, **degranulation**, and **release of histamine** and other chemical mediators (eg, prostaglandin, leukotrienes).

Although multiple chemical mediators play a role in anaphylaxis, histamine is believed to cause the most significant, broad-ranging effects, including the following:

- H₁ and H₂ receptor stimulation results in **vasodilation** (causing **hypotension**) and increased catecholamine secretion (causing **tachycardia**).

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- H₁ receptor stimulation causes increased bronchial smooth muscle contraction (resulting in **bronchoconstriction** and wheezing) and **increased vascular permeability** (worsening hypotension and contributing to urticaria).
- H₂ receptor stimulation increases gastric acid secretion, which contributes to gastrointestinal symptoms (eg, nausea, vomiting).

In addition, histamine can activate peripheral nociceptive receptors, causing pruritus or pain. To mitigate its widespread effects, an antihistamine is often given as adjunct treatment in anaphylaxis after mainstay treatment with intramuscular epinephrine.

(Choice A) Gram-negative bacterial endotoxins are the most potent mediators of gram-negative sepsis. Although sepsis can present with hypotension, tachycardia, and respiratory symptoms, children with sepsis typically have fever, and the onset of symptoms occurs over hours to days (vs minutes). In addition, wheals are not expected.

(Choice B) Gram-positive bacterial enterotoxin is the cause of staphylococcal food poisoning, which can cause vomiting, diarrhea, and abdominal cramps. However, symptoms typically occur 2-8 hours after ingestion (vs immediately) of contaminated food, and wheezing and wheals are not expected.

(Choice C) Kallikrein-generated bradykinin plays a role in bradykinin-mediated angioedema (eg, hereditary, ACE inhibitor-related), which can cause bowel wall edema and result in nausea, vomiting, or diarrhea. In contrast to mast cell-mediated angioedema, bradykinin-mediated angioedema does not typically cause bronchospasm, urticaria, or hypotension.

(Choice E) Vasoactive intestinal polypeptide is secreted by VIPomas, rare functioning neuroendocrine tumors most often located in the pancreas. VIPomas can cause watery diarrhea, nausea, and vomiting; however, acute-

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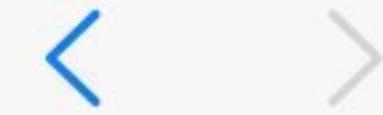
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(Choice E) Vasoactive intestinal polypeptide is secreted by VIPomas, rare functioning neuroendocrine tumors most often located in the pancreas. VIPomas can cause watery diarrhea, nausea, and vomiting; however, acute-onset hypotension, wheezing, and wheals are not expected.

Educational objective:

Anaphylaxis is an IgE-mediated response to an allergen that results in the release of histamine by mast cells and basophils. Histamine causes widespread physiologic effects, including vasodilation and increased vascular permeability (eg, hypotension), increased catecholamine secretion (eg, tachycardia), and bronchoconstriction (eg, wheezing).

References

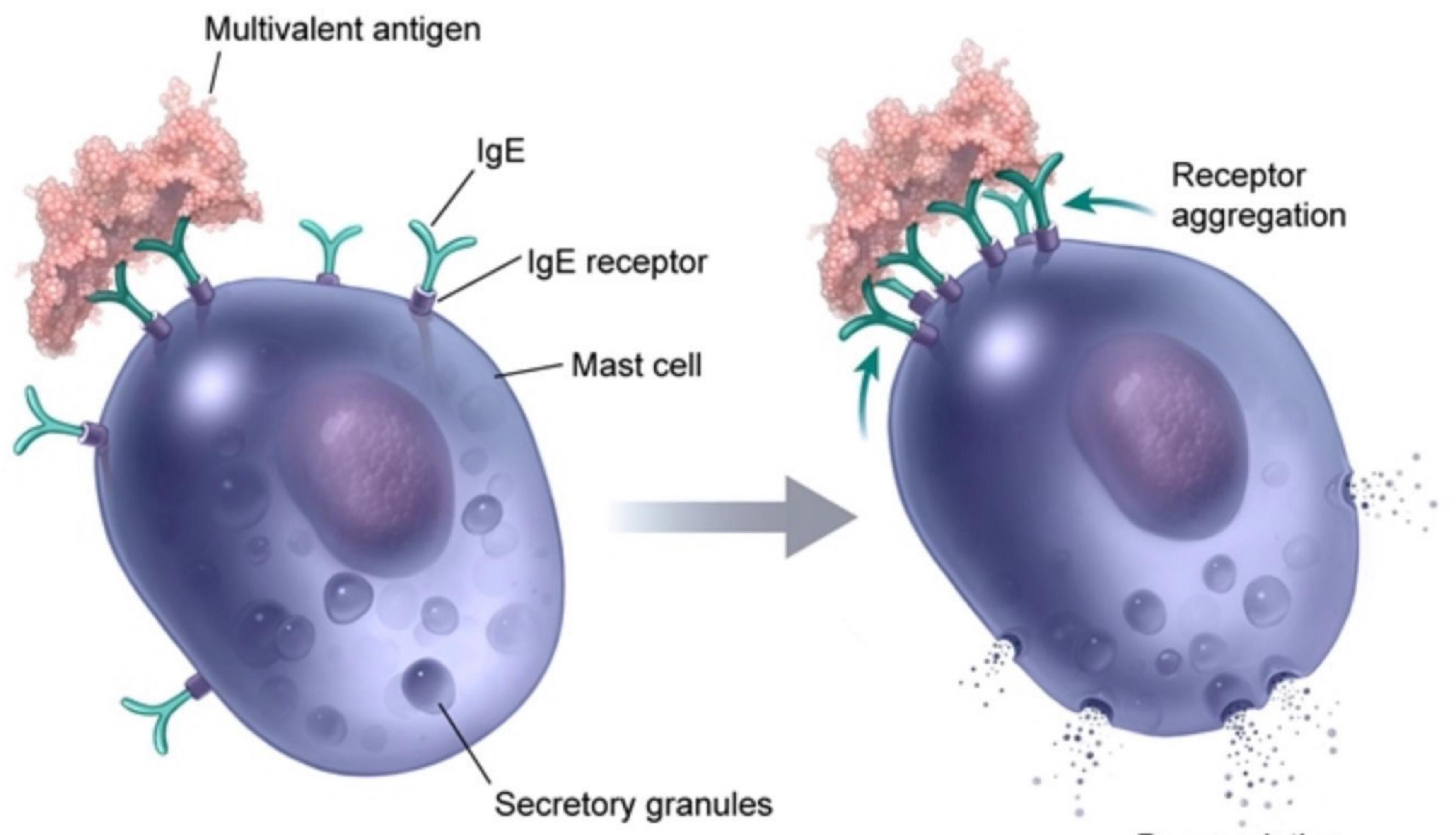


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High-affinity IgE receptor activation



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- H₁ and H₂ receptor stimulation results in **vasodilation** (causing **hypotension**) and increased catecholamine secretion (causing **tachycardia**).
- H₁ receptor stimulation causes increased bronchial smooth muscle contraction (resulting in **bronchoconstriction** and wheezing) and **increased vascular permeability** (worsening hypotension and contributing to urticaria).



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A 19-year-old woman comes to the office to discuss treatment options for seasonal sneezing, rhinorrhea, and nasal congestion. She has had these symptoms for the past few springs and summers but is now willing to "try anything" to allow her to concentrate on her upcoming final exams. The patient has no significant medical history, takes no medications, and has no drug allergies. Vital signs are within normal limits and physical examination reveals mild bilateral pale and boggy nasal turbinates with copious clear mucus. Fluticasone, an intranasal glucocorticoid, is prescribed. Which of the following is the most likely mechanism of action of this drug?

- A. Apoptosis of tissue eosinophils (29%)
- B. Antagonism of leukotriene receptors (32%)
- C. Binding and removal of circulating IgE (12%)
- D. Reduced differentiation of regulatory T cells (Treg) (25%)

Omitted

Correct answer

A



29%

Answered correctly



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Explanation

Anti-inflammatory effects of glucocorticoids

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Anti-inflammatory effects of glucocorticoids

The diagram illustrates the anti-inflammatory actions of glucocorticoids. It shows a cell membrane with various targets for these hormones. Inside the cell, the nucleus contains DNA and NF-κB. The cytoplasm contains Phospholipase A2, Annexin-1, and mitochondria with Bcl-2.

Glucocorticoids bind to a **Glucocorticoid receptor** in the cytoplasm, which then enters the **Nucleus** to bind to **DNA**, inhibiting the **NF-κB** complex. This leads to:

- ↓ Inflammation**: Reduces the release of **Arachidonic acid**, **Prostaglandin**, and **Leukotrienes**.
- ↓ Leukocyte immigration**
- ↑ Eosinophil apoptosis**
- ↑ Annexin-1**
- ↑ Anti-inflammatory cytokines (eg, IL-10)**
- ↓ Inflammatory cytokines (eg, IFN-γ, IL-1, TNF-α)**
- ↓ Bcl-2** (in mitochondria)

Phospholipase A2 is inhibited by the reduced arachidonic acid levels. Annexin-1 promotes apoptosis of eosinophils. Bcl-2 is downregulated in the mitochondria, leading to increased apoptosis.

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This patient with allergic rhinitis has been prescribed fluticasone, an intranasal **glucocorticoid**.

Glucocorticoids bind to cytoplasmic receptors and translocate to the nucleus where they **inhibit transcription** of genes that encode **inflammatory mediators** and decrease immune cell survival and propagation. This results in wide-ranging effects that **suppress** immunostimulatory activity of all **leukocyte cell lines**, including the following:

- Decreased tissue production of proinflammatory prostaglandins and leukotrienes through the inhibition of phospholipase A₂
- Decreased synthesis of almost all proinflammatory cytokines, with increased anti-inflammatory cytokine (eg, IL-10) production
- Impaired macrophage activation and neutrophil emigration
- Increased **apoptosis of eosinophils**, T cells, and monocytes, perhaps by decreasing *Bcl-2* expression

Glucocorticoids also act on nonimmune cells in the nose (including epithelial cells, goblet cells, and vascular endothelial cells) to decrease uptake of allergen particles, decrease mucus production, and decrease vascular permeability.

(Choice B) Mast cells and eosinophils release cysteinyl-containing leukotrienes (leukotriene C₄, D₄, and E₄) that trigger mucus secretion and edema. Cysteinyl leukotriene receptor antagonists (eg, montelukast, zafirlukast) block these leukotriene-mediated effects to improve symptoms of allergic rhinitis.

(Choice C) The anti-IgE antibody omalizumab binds circulating IgE to decrease serum IgE levels and limit the allergen-induced immunologic response.

(Choice D) In addition to inducing T cell apoptosis, glucocorticoids also promote (not reduce) differentiation of T

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phospholipase A₂

- Decreased synthesis of almost all proinflammatory cytokines, with increased anti-inflammatory cytokine (eg, IL-10) production
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(Choice C) The anti-IgE antibody omalizumab binds circulating IgE to decrease serum IgE levels and limit the allergen-induced immunologic response.

(Choice D) In addition to inducing T cell apoptosis, glucocorticoids also promote (not reduce) differentiation of T cells into regulatory subsets. These **regulatory T cells** (Treg) decrease the immune response to allergens partly by producing IL-10, which inhibits macrophage function and downregulates expression of major histocompatibility complex (MHC) class II on antigen-presenting cells.

Educational objective:

Glucocorticoids inhibit transcription of proinflammatory mediators and promote apoptosis of eosinophils, T cells, and monocytes.

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• Impaired macrophage activation and neutrophil migration

• Increased vascular permeability

Glucocorticoids increase endothelial permeability

(Choice B) Glucocorticoids trigger mucosal block these

(Choice C) Allergen-induced T cells into regulatory cells by producing histocompatibility

(Choice D) Education Glucocorticoids and monocytes

Immunology Subject System Topic

Exhibit Display

CD4+ T cell differentiation

The diagram illustrates the differentiation of CD4+ Th0 cells into four distinct subsets: Th1, Th2, Th17, and Treg, each associated with specific cytokine profiles and biological functions.

- Th1 Differentiation:** Triggered by IL-12. Associated cytokines: IFN- γ , TNF- β , IL-2. Functions: Viral/bacterial defense, T-cell & APC activation.
- Th2 Differentiation:** Triggered by IL-4. Associated cytokines: IL-4, IL-5, IL-10, IL-13. Functions: Humoral/nematode defense, B-cell/eosinophil activation.
- Th17 Differentiation:** Triggered by TGF- β and IL-6. Associated cytokines: IL-17A/F, IL-21, IL-22. Functions: Bacterial defense/autoimmunity, Neutrophil activation/recruitment.
- Treg Differentiation:** Triggered by TGF- β and FOXP3. Associated cytokines: IL-10, TGF- β . Functions: Immune downregulation, Tolerance.

APC (Antigen-Presenting Cell) is shown interacting with the CD4+ Th0 cell.

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Exhibit Display

Regulatory T-cell function

The diagram illustrates the regulatory functions of a Treg cell. It branches into three main pathways:

- Pathway 1 (Left):** Treg secretes IL-10, which acts on an APC (represented by a green cell with blue nucleus). The effect is labeled \downarrow MHC II expression and \downarrow APC activity.
- Pathway 2 (Middle):** Treg secretes TGF- β , which acts on an APC. The effect is labeled \uparrow FOXP3 and \uparrow Treg production.
- Pathway 3 (Right):** Treg expresses CTLA-4 on its surface. This signal, along with CD28, acts on a Dendritic cell (represented by a grey cell with blue nucleus). The effect is labeled CD80/86 and \downarrow T cell activation.

Activated B cells are also shown in the diagram.

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Immunology Subject System Topic

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A 7-year-old boy is brought to the office due to sudden onset of facial swelling 2 hours ago. He has had no itching or pain other than a sore throat over the last 2 days, for which he has taken acetaminophen. The patient has had similar episodes of facial swelling that resolved spontaneously after a few days. Temperature is 37 C (98.6 F), blood pressure is 100/78 mm Hg, pulse is 95/min, and respirations are 24/min. Examination shows nonpitting edema of the cheeks, lips, and tongue; there is no tenderness or erythema. Which of the following studies is most likely to be abnormal?

- A. Eosinophil count (6%)
- B. Serum C4 level (58%)
- C. Serum C8 level (2%)
- D. Serum IgA level (12%)
- E. Serum IgE level (20%)

Omitted

Correct answer

B



58%

Answered correctly



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Explanation

Hereditary angioedema

C1

Kininogen

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Hereditary angioedema

```
graph TD; C1[C1] --> ActivatedC1[Activated C1]; C1 --> C1InhibitorDeficiency[C1 inhibitor deficiency]; C1InhibitorDeficiency --> ActivatedC1; Kininogen[Kininogen] --> Kallikrein[Kallikrein]; Kallikrein --> Bradykinin[Bradykinin]; Bradykinin --> Angioedema[Angioedema without urticaria]; Bradykinin --> ACE[ACE*]; ACE --> InactiveProducts[Inactive products]; C1InhibitorDeficiency --> C4Consumption[↑ C4 consumption (low C4 levels)];
```

*ACE inhibitors exacerbate angioedema attacks.

This patient's recurrent facial swelling is most likely due to **hereditary angioedema**, which is characterized by a **deficiency** or dysfunction of **C1 inhibitor** (previously referred to as C1 esterase inhibitor). Poor C1 inhibitor function leads to elevated bradykinin, a peptide that causes vasodilation and increased vascular permeability, resulting in edema.

Presentation is typically in childhood or adolescence with episodes of **swelling** affecting the skin (eg, face, extremities) and mucosa of the gastrointestinal tract and/or larynx. Attacks are often precipitated by minor trauma (eg, dental procedure) or emotional stress and are **not associated** with itching or urticaria.

Initial evaluation of hereditary angioedema is with **complement** testing. **Low C4** is characteristic because, in the absence of C1 inhibitor, unregulated activation of C1 leads to **excess activated C1** and, in turn, unchecked

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Presentation is typically in childhood or adolescence with episodes of **swelling** affecting the skin (eg, face, extremities) and mucosa of the gastrointestinal tract and/or larynx. Attacks are often precipitated by minor trauma (eg, dental procedure) or emotional stress and are **not associated** with itching or urticaria.

Initial evaluation of hereditary angioedema is with [complement](#) testing. **Low C4** is characteristic because, in the absence of C1 inhibitor, unregulated activation of C1 leads to **excess activated C1** and, in turn, unchecked cleavage of C4. Diagnosis is confirmed by a decrease in functional C1 inhibitor level.

(Choices A and E) Elevated eosinophils and IgE are associated with allergic conditions. In contrast to bradykinin-mediated hereditary angioedema, allergic angioedema (eg, anaphylaxis) is due to histamine release from activated mast cells and presents with pruritis and urticaria in addition to swelling.

(Choice C) C8 is involved in the formation of the membrane attack complex, which, when deficient, results in increased susceptibility to *Neisseria* infections. Deficiency of terminal complement components (C5, C6, C7, C8, C9) does not occur with hereditary angioedema because the upstream complement fragments (C2b, C4b) are rapidly inactivated in the plasma.

(Choice D) Selective IgA deficiency increases risk for anaphylaxis, which can cause angioedema. However, this risk is only with transfusion of blood products and would present with other organ system involvement (eg, bronchospasm, hypotension, urticaria). IgA deficiency is also associated with certain autoimmune conditions (eg, celiac disease, systemic lupus erythematosus), but none of these would present with isolated facial swelling.

Educational objective:

Hereditary angioedema is characterized by recurrent episodes of cutaneous and/or mucosal swelling due to C1 inhibitor deficiency. C4 levels are low due to uninhibited cleavage of C4 by excess activated C1.

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Presentation is typically in childhood or adolescence with episodes of **swelling** affecting the skin (eg. face, extremities) or mucous membranes. There may be a history of **trauma** (eg. insect bites).

Initial evaluation should include a history and physical examination, and laboratory tests to rule out other causes of swelling.

(Choices A-C) IgG antibodies are present in the serum of patients with C1q deficiency. IgG antibodies bind to bacteria, activating the classical pathway. This leads to the formation of C3a (anaphylatoxin), which causes mast cell degranulation and histamine release, leading to increased vascular permeability and edema. C3a also acts as an opsonin, promoting phagocytosis by neutrophils. C3b is a membrane attack complex component that can bind to the bacterial surface, forming a pore that allows water to enter the cell, leading to lysis.

(Choice D) IgG antibodies are present in the serum of patients with C1q deficiency. IgG antibodies bind to bacteria, activating the classical pathway. This leads to the formation of C3a (anaphylatoxin), which causes mast cell degranulation and histamine release, leading to increased vascular permeability and edema. C3a also acts as an opsonin, promoting phagocytosis by neutrophils. C3b is a membrane attack complex component that can bind to the bacterial surface, forming a pore that allows water to enter the cell, leading to lysis.

(Choice E) IgG antibodies are present in the serum of patients with C1q deficiency. IgG antibodies bind to bacteria, activating the classical pathway. This leads to the formation of C3a (anaphylatoxin), which causes mast cell degranulation and histamine release, leading to increased vascular permeability and edema. C3a also acts as an opsonin, promoting phagocytosis by neutrophils. C3b is a membrane attack complex component that can bind to the bacterial surface, forming a pore that allows water to enter the cell, leading to lysis.

Exhibit Display

Complement pathways

The diagram illustrates the three main complement pathways: Classical, Alternative, and Lectin.
1. **Classical Pathway:** IgG antibodies bind to bacteria. The C1 complex (q,r,s) cleaves C2 and C4. The C3 convertase (C2b3b) is formed, cleaving C3 into C3a (anaphylatoxin) and C3b (opsonin). C3b binds to the bacterial surface. C5 is cleaved by C3 convertase into C5a (anaphylatoxin) and C5b, which forms the Membrane Attack Complex (C6-9) with C6-9.
2. **Alternative Pathway:** Factor B/D converts C3 into C3b. C3b binds to the bacterial surface. C3 convertase (C2b3b) is formed, cleaving C3 into C3a (anaphylatoxin) and C3b (opsonin). C3b binds to the bacterial surface. C5 is cleaved by C3 convertase into C5a (anaphylatoxin) and C5b, which forms the Membrane Attack Complex (C6-9) with C6-9.
3. **Lectin Pathway:** Mannose-rich moieties on bacteria bind to the C1-like complex (MBL, MASP). This triggers the cleavage of C2 and C4. The C3 convertase (C2b3b) is formed, cleaving C3 into C3a (anaphylatoxin) and C3b (opsonin). C3b binds to the bacterial surface. C5 is cleaved by C3 convertase into C5a (anaphylatoxin) and C5b, which forms the Membrane Attack Complex (C6-9) with C6-9.

MASP = mannose-associated serine protease; MBL = mannose-binding lectin.

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An 11-year-old girl is brought to the office for a health maintenance visit. She feels well and has no chronic medical conditions. As part of routine care, the patient receives a first dose of the quadrivalent meningococcal conjugate vaccine and the 9-valent human papillomavirus vaccine. Five minutes later, while being escorted to the waiting area, the patient appears pale and reports feeling dizzy. She immediately loses consciousness, but a fall is prevented by the health care provider. Blood pressure is 70/40 mm Hg and pulse is 46/min. On physical examination, the patient has normal lung and heart sounds. There is no rash. Which of the following is the most likely cause of this patient's syncope?

- A. Delayed-type hypersensitivity reaction to the vaccine (0%)
- B. Excessive cytokine response to vaccine microbial components (21%)
- C. IgE-mediated hypersensitivity reaction to vaccine allergen (19%)
- D. Stress-induced cardioinhibitory and vasodepressor response (57%)
- E. Systemic invasion by live attenuated microbial agents (0%)

Omitted
Correct answer
D

57%
Answered correctly

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Explanation

Vaccine-related hypotension &/or syncope

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Vaccine-related hypotension &/or syncope		
	Vasovagal syncope	Anaphylaxis
Trigger	<ul style="list-style-type: none">Pain or emotional distress	<ul style="list-style-type: none">Vaccine antigen
Mechanism	<ul style="list-style-type: none">Vagally mediated cardioinhibitory & vasodepressor response	<ul style="list-style-type: none">IgE-mediated response leading to widespread release of inflammatory mediators (eg, histamine)
Clinical presentation	<ul style="list-style-type: none">Prodrome (eg, pallor, nausea, diaphoresis)Hypotension with bradycardiaRapid resolution	<ul style="list-style-type: none">Urticaria, flushingHypotension with tachycardiaWheezingProgressive symptoms
Management	<ul style="list-style-type: none">Lying supine with legs elevated	<ul style="list-style-type: none">Immediate epinephrine

This patient most likely experienced **vasovagal syncope**, which involves a pain-induced or an emotional distress–induced **cardioinhibitory and vasodepressor** response. **Vaccine administration** is a known precipitant of vasovagal syncope, especially in adolescents. Because syncope-related falls can lead to serious injury (eg, skull fractures, intracranial hemorrhage), patients should be closely monitored for 15 minutes following vaccine administration.

Patients with vasovagal syncope typically experience a **prodrome** (eg, pallor, nausea, diaphoresis) prior to losing consciousness. The mechanism is not well understood, but the trigger, in combination with a state of orthostatic stress (eg, upright posture, dehydration), is believed to signal the CNS to decrease sympathetic activity and increase parasympathetic tone, overriding the [normal baroreceptor response](#). This leads to

~~bradycardia, reduced IV contractility, and decreased peripheral vascular resistance, resulting in hypotension.~~

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activity and increase parasympathetic tone, overriding the [normal baroreceptor response](#). This leads to **bradycardia**, reduced LV contractility, and decreased peripheral vascular resistance, resulting in **hypotension**, decreased cerebral perfusion, and, ultimately, syncope. Symptoms rapidly resolve within 1-2 minutes.

Postvaccination syncope can be confused with anaphylaxis, a rare but serious adverse effect resulting from IgE-mediated hypersensitivity to a vaccine component (eg, egg or yeast proteins). Anaphylaxis can develop rapidly following vaccination and may cause hypotension and syncope; however, affected patients typically experience urticaria or flushing rather than pallor, respiratory symptoms (eg, upper airway edema, bronchospasm), and reflex tachycardia rather than bradycardia (**Choice C**).

(Choice A) Delayed-type reactions are due to the direct action of sensitized T cells when stimulated by contact with an antigen. They occur hours to days, rather than minutes, after exposure and typically present with a rash.

(Choice B) An excessive cytokine response to the microbial components of a vaccine can result in a self-limiting local reaction (eg, redness or pain at the vaccination site) or, sometimes, systemic symptoms (eg, fever, malaise).

(Choice E) The administration of a [live attenuated vaccine](#) (eg, measles, mumps, and rubella) to an immunocompromised host may cause uncontrolled replication and systemic invasion of the virus. Symptoms of an active infection would not manifest until >12-24 hours. Neither the meningococcal nor the HPV vaccine is live, and this patient is not immunocompromised.

Educational objective:

Vasovagal syncope is a known complication of vaccine administration, particularly in adolescents. It typically involves a prodrome and can be differentiated from anaphylaxis based on skin findings (pallor vs urticaria), absence of respiratory symptoms (eg, upper airway edema, bronchospasm), and presence of bradycardia (vs tachycardia).

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• Prodrome (eg, pallor, nausea, • Urticaria, flushing

Clinical presentation

Management

This patient is experiencing distress-in-pain, which is a common precipitant of anaphylaxis. Injury (eg, bite, sting, vaccine adverse effect) can also trigger anaphylaxis.

Patients with anaphylaxis are losing consciousness due to orthostatic hypotension. Physical activity and exercise can cause bradycardia and syncope, leading to decreased blood pressure.

Postvaccination anaphylaxis is mediated by IgE antibodies following vaccination. Urticaria or hives are common symptoms of anaphylaxis. The reflex tachycardia rather than bradycardia (Choice C).

Exhibit Display

Baroreceptor reflex in response to decreased blood pressure

The diagram illustrates the baroreceptor reflex in response to decreased blood pressure. It shows the heart, brain, and spinal cord. Arrows indicate the flow of information from the heart's SA and AV nodes, through the myocardium, up to the brainstem's cardioregulatory center. From there, signals travel down to the heart via parasympathetic fibers (decreasing heart rate and contractility) and sympathetic fibers (increasing heart rate and contractility). The diagram is labeled with numbered callouts:

- 1 Baroreceptors ↓ firing
- 2 Sensory fibers ↓ signaling
- 3 Parasympathetic fibers ↓ signaling
Sympathetic fibers ↑ signaling
- 4 ↑ Heart rate & contractility
Vasoconstriction

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(Choice A) Delayed-type reactions are due to the direct action of sensitized T cells when stimulated by contact

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Postvaccination syncope can be confused with anaphylaxis, a rare but serious adverse effect resulting from IgE-mediated hypersensitivity.

following vasodilation, urticaria or reflex tachycardia.

(Choice A) with an antihistamine.

(Choice B) local reaction (e.g., malaise).

(Choice C) immunocompetent, an active infection, live, and the patient.

Education
Vasovagal syncope involves a brief absence of consciousness, tachycardia, and hypotension.

Reference

- Vaccine-associated hypersensitivity.
- Syncope: epidemiology, etiology, and prognosis.

Exhibit Display

Vaccine types	
Live attenuated vaccines	Nonlive (toxoid, subunit, conjugate, inactivated) vaccines
<ul style="list-style-type: none">Polio (oral)*Measles, mumps & rubellaRotavirusYellow feverVaricella, zoster	<ul style="list-style-type: none">Influenza (intramuscular)PneumococcusDiphtheria–tetanus–pertussisTyphoidHepatitis AHepatitis B<i>Haemophilus influenzae</i> type b
<small>*Not available in the United States; advised only for developing countries.</small>	

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A 36-year-old woman with fistulizing perianal Crohn disease comes to the office for a follow-up appointment. Eight weeks ago, the patient began receiving intermittent injections of infliximab, a chimeric human-mouse monoclonal antibody targeted against tumor necrosis factor-alpha. She reports improvement in fistula discharge and discomfort but has experienced fever, diffuse joint pain, and an itchy rash 5-7 days after each of the recent treatments. The symptoms spontaneously resolve after 2-3 days. The patient has no other medical conditions and has no history of drug allergies. A delayed drug reaction due to formation of antibodies against foreign drug components is suspected. Which of the following mechanisms is most likely responsible for resolution of these drug reactions?

- A. Activation of the mononuclear phagocyte system (24%)
- B. Apoptosis of tissue mast cells and eosinophils (4%)
- C. Clearance of intact drug molecules by kidneys (16%)
- D. Endocytosis and degradation of mast cell-bound IgE (12%)
- E. Regulatory T-cell-mediated cytotoxic T-cell suppression (42%)

Omitted
Correct answer
A

24%
Answered correctly

02 secs
Time Spent

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Explanation

Chimeric monoclonal antibodies such as infliximab contain amino acid sequences from human and **non-**

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Chimeric monoclonal antibodies such as infliximab contain amino acid sequences from human and **non-human** (eg, mice) sources. These proteins are processed by antigen presenting cells, displayed on class II major histocompatibility complexes, and the nonhuman components are **recognized as foreign** by patrolling CD4 cells. The CD4 cells then stimulate activated B-cells to undergo somatic hypermutation and class switching, which generates plasma cells that secrete high-affinity **IgG antibodies against foreign components** of the drug.

With subsequent infusions, the foreign proteins in the medication trigger memory B cells to differentiate into plasma cells, which generate a burst of IgG against the monoclonal antibody. Binding of the IgG to the medication generates **immune complexes** (ICs), which are then **cleared by mononuclear phagocytes** in the reticuloendothelial system, as follows:

- **Classic complement activation:** The Fc portion of the bound IgG activates the [classical complement system](#), leading to the generation of C3b on the IC. C3b binds to CR1 on erythrocytes/leukocytes, which bring the IC to reticuloendothelial mononuclear phagocytes (eg, Kupffer cells, splenic macrophages) for clearance.
- **Direct removal:** Mononuclear phagocytes bind to the Fc portion of the bound IgG using their Fc receptor (CD16) and remove the IC from the circulation.

IC clearance generally proceeds without issue, but significant quantities of ICs can saturate the phagocytic system and lead to IC aggregation; IC aggregates can deposit in tissue (eg, skin, joints), where persistent complement activation can result in a [type III hypersensitivity](#) reaction called **serum sickness**. This is typically marked by fever, urticarial rash, and joint pain **5-14 days** after exposure. Most cases **resolve spontaneously** over days as mononuclear phagocytes continue to remove the excess ICs.

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(CD10) and remove the IC from the circulation.

IC clearance generally proceeds without issue, but significant quantities of ICs can saturate the phagocytic system and lead to IC aggregation; IC aggregates can deposit in tissue (eg, skin, joints), where persistent complement activation can result in a [type III hypersensitivity](#) reaction called **serum sickness**. This is typically marked by fever, urticarial rash, and joint pain **5-14 days** after exposure. Most cases **resolve spontaneously** over days as mononuclear phagocytes continue to remove the excess ICs.

(Choice B) Glucocorticoids trigger apoptotic cell death of eosinophils and tissue mast cells in patients with allergic conditions (eg, asthma). Apoptosis, a form of programmed cell death, is not typically associated with degranulation or allergic symptoms.

(Choices C and D) Antibodies are too large to be cleared from the bloodstream through fenestrations in the liver or kidney. Instead, they are typically removed via endocytosis or phagocytosis after binding Fc receptors on the surface of immune cells (eg, macrophages, eosinophils, mast cells). Endocytosis and degradation of mast cell-bound IgE occurs with type I hypersensitivity reactions (which occur within minutes, not days later); in addition, this process is only responsible for removing tiny amounts of IgE (not ICs) from the body.

(Choice E) Regulatory T cells downregulate the cytotoxic T-cell response. Although cytotoxic T cells mediate Stevens-Johnson syndrome (destruction of keratinocytes that are displaying drug antigens), they do not play a role in the development of serum sickness.

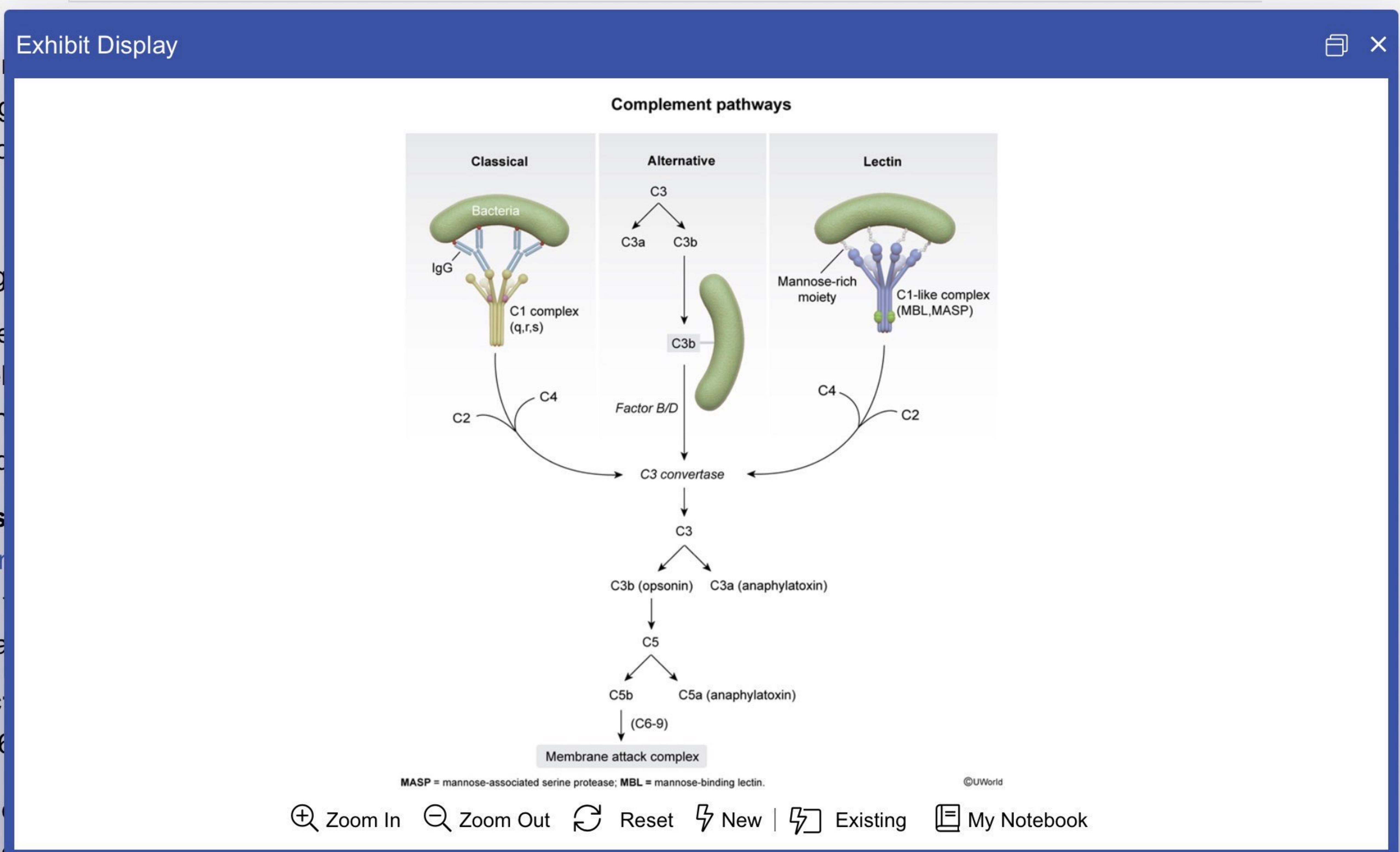
Educational objective:

Serum sickness is an immune complex-mediated type III hypersensitivity reaction that typically forms 5-14 days after exposure to foreign proteins in an antitoxin, antivenom, monoclonal antibody, or vaccine. Patients typically develop fever, urticarial rash, and arthralgia that resolve spontaneously over days as the immune complexes are cleared by the mononuclear phagocyte system.

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Explanation



IC clearance system and complement activation can result in a type III hypersensitivity reaction called **serum sickness**. This is typically marked by fever, urticarial rash, and joint pain **5-14 days** after exposure. Most cases **resolve spontaneously** over days or months unless phagocytes continue to remove the excess ICs.

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A 21-year-old woman comes to the office due to recurrent episodes of self-limited, colicky abdominal pain. She also had an episode of facial swelling that resolved spontaneously. The patient has no other significant past medical history and takes no medications. Examination is unremarkable. Evaluation shows that her complement protein C1, even when not attached to an antigen-antibody complex, is excessively cleaving C2 and C4. Which of the following is most likely increased in this patient?

- A. Antinuclear antibody titer (20%)
- B. Antistreptolysin O titer (7%)
- C. Bradykinin (61%)
- D. Free hemoglobin (7%)
- E. Renin (2%)

Omitted
Correct answer
C

61%
Answered correctly

06 secs
Time Spent

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Version

Explanation

This patient with recurrent episodes of abdominal pain and an episode of facial swelling likely has angioedema due to **C1 inhibitor (C1INH) deficiency**. C1INH prevents C1-mediated cleavage of C2 and C4, thereby limiting activation of the complement cascade. It also blocks kallikrein-induced conversion of kininogen to **bradykinin**, a potent vasodilator that also causes increased vascular permeability.

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Acquired or hereditary **C1INH deficiency** (due to the complete absence of C1INH or the presence of a dysfunctional variant or an anti-C1INH antibody) leads to elevated levels of bradykinin, and patients can develop **bradykinin-associated angioedema**. Symptoms include facial swelling (without urticaria), life-threatening laryngeal edema, and gastrointestinal manifestations (eg, nausea/vomiting, colicky pain, diarrhea). Management of acute attacks involves supportive care and the administration of C1INH concentrate or a kallikrein inhibitor.

(Choice A) Increased antinuclear antibody (ANA) titers are seen in a number of autoimmune conditions, including systemic lupus erythematosus, which is associated with hypocomplementemia but would have different clinical manifestations (eg, butterfly rash, arthritis, oral ulcers). ANA production is not a result of excessive C1 activity.

(Choice B) Poststreptococcal glomerulonephritis is associated with increased antistreptolysin O titers, complement activation, and low levels of C3. The typical presentation is hematuria or nephritic syndrome following respiratory infection.

(Choice D) Complement-mediated intravascular hemolysis can result from autoantibodies (autoimmune hemolytic anemia) or from direct complement activation (paroxysmal nocturnal hemoglobinuria); however, neither condition results from excessive C1 activity.

(Choice E) Angiotensin-converting enzyme (ACE) inhibitors, which are associated with idiopathic angioedema, function by blocking ACE and result in increased renin levels. ACE also degrades bradykinin.

Educational objective:

C1 inhibitor (C1INH) deficiency causes increased cleavage of C2 and C4 and results in inappropriate activation of the complement cascade. C1INH also blocks kallikrein-induced conversion of kininogen to bradykinin, a potent vasodilator associated with angioedema.

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Omitted
Correct answer: C

Exhibit Display

Causes of angioedema

	Causes of angioedema	
Mast cell activation	<ul style="list-style-type: none">Type 1 hypersensitivity reactions (IgE-mediated)Direct mast cell activation (eg, opioids)	Associated pruritus & urticaria
Excess bradykinin	<ul style="list-style-type: none">ACE inhibitorsC1 inhibitor deficiency (hereditary/acquired)	No pruritus or urticaria

This patient due to C1 activation of potent vas...
Acquired or dysfunction bradykinin- laryngeal edema of acute at...
(Choice A) including s... clinical man... activity.
(Choice B) compleme... following respiratory infection.
(Choice D) Complement-mediated intravascular hemolysis can result from autoantibodies (autoimmune

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Autoimmune diseases