ANGIOEDEMA: A REVIEW OF ACUTE MANAGEMENT

A presentation for HealthTrust Members
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Speaker Disclosures

* **The presenter and their preceptor have no financial relationships with any commercial interests pertinent to this presentation.**

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Learning Objectives

Describe	Describe the different types of angioedema and the corresponding pathophysiologic features
Explain	Explain the mechanisms of action for medications used to treat angioedema
Identify	Identify the place in therapy of the pharmacologic options for the treatment of angioedema.

BACKGROUND

What is Angioedema?

"Swelling of the subcutaneous tissues due to increased vascular permeability and extravasation of intravascular fluid"

Lips, tongue, eyes, hands, feet, genitals

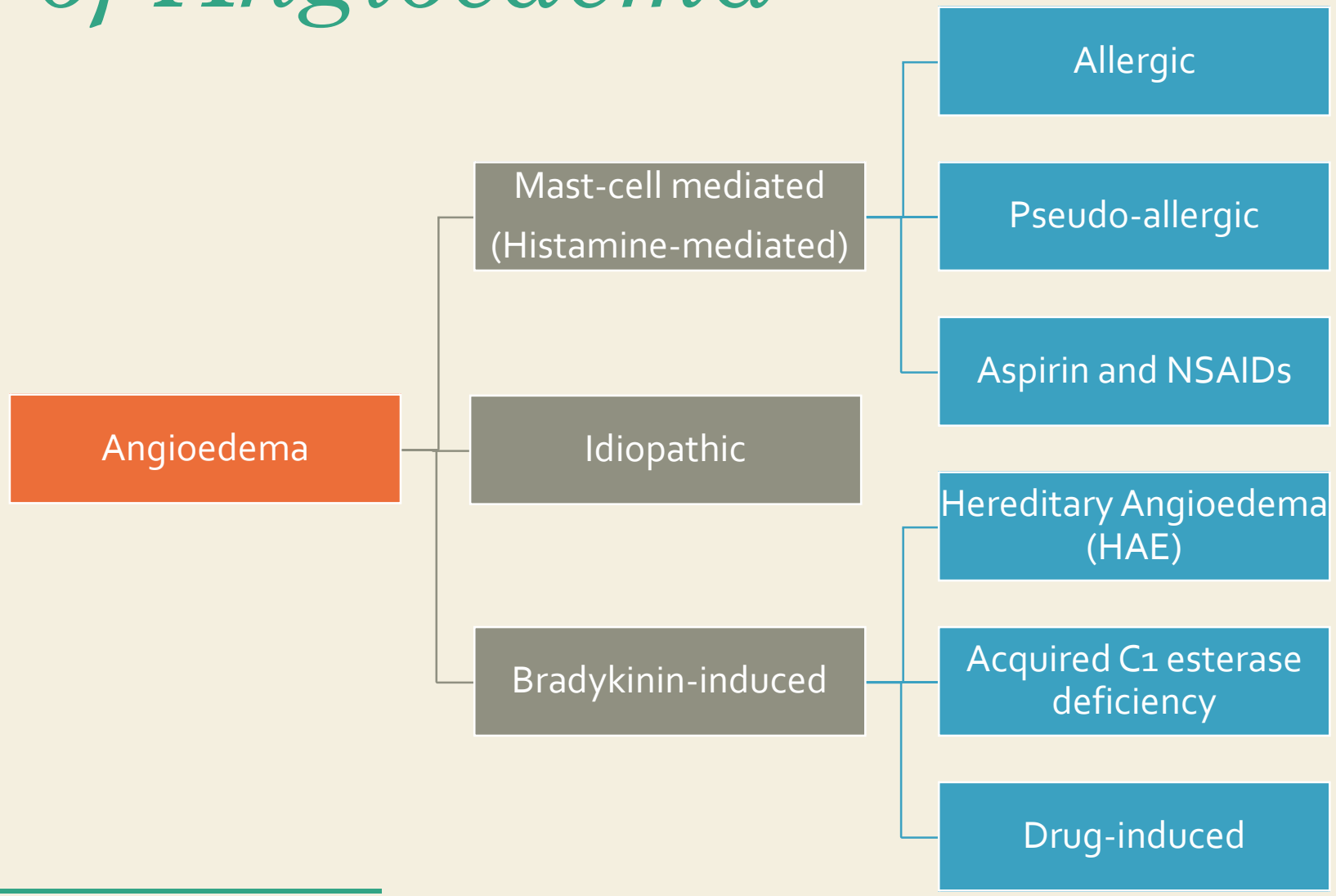
Acute or chronic

Exposure, genetics, or idiopathic

Bradykinin or mast-cell mediators

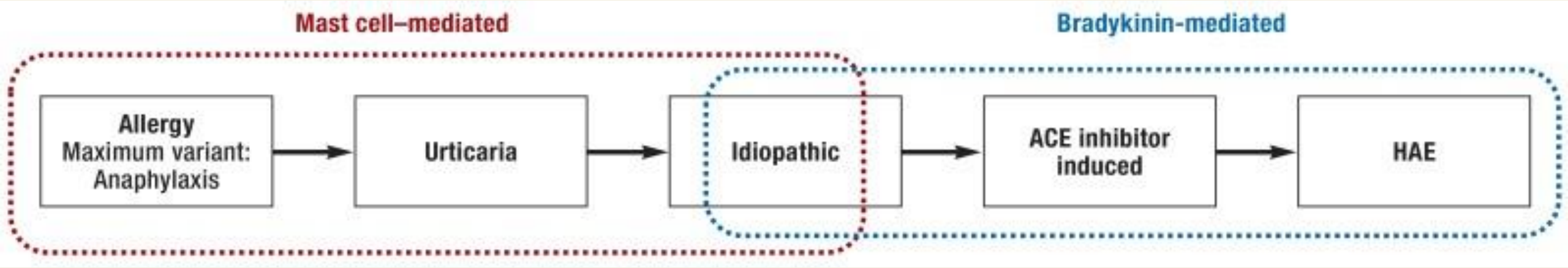
Source: Angioedema. In: Merck Manuals Professional Edition. [Internet]

Types of Angioedema



Sources: *Dtsch Arztebl Int*. 2017 Jul; 114(29-30): 489-96.
Acad Emerg Med. 2014 Apr;21(4):469-84.

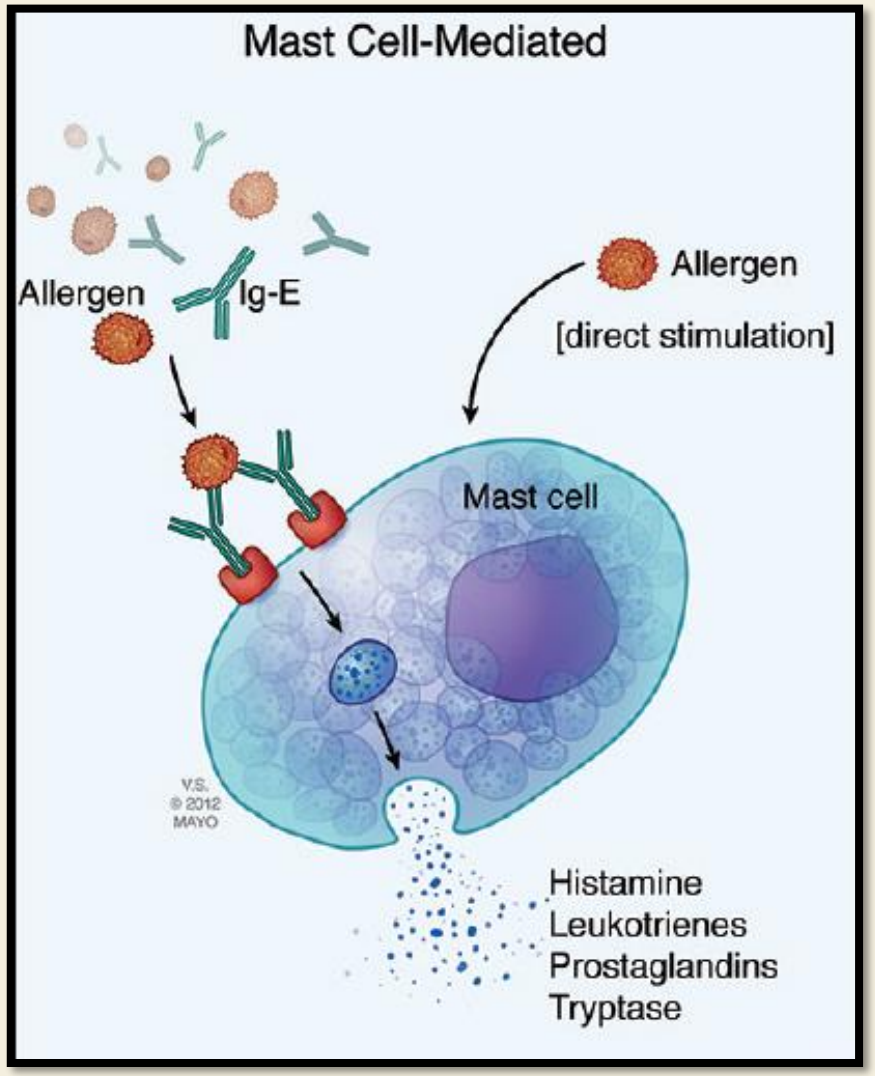
Epidemiology



Most common

Least common

Source: *Dtsch Arztebl Int*. 2017 Jul; 114(29-30): 489-96.



Mast Cell-Mediated: Pathophysiology

- Activation of mast cells or basophils
- Histamine release
- Vasodilation
- Increased vascular permeability
- Edema

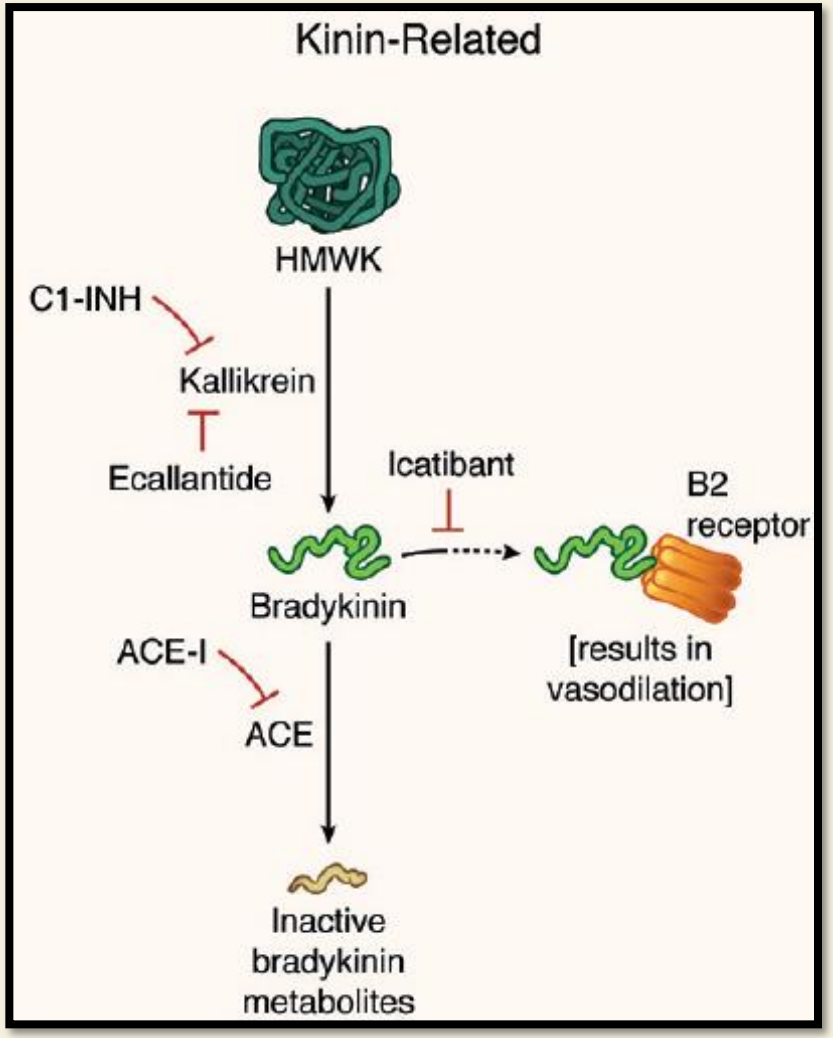
Causes of mast cell activation: allergens, NSAIDs, fibrinolytics

Sources: *Indian J Anaesth.* 2016;60(8):534-41.

Dtsch Arztebl Int. 2017 Jul; 114(29-30): 489-96.

Bradykinin-Induced: Pathophysiology

- Bradykinin
- Bradykinin B2 receptor
- Vasodilation
- Increased vascular permeability
- Edema

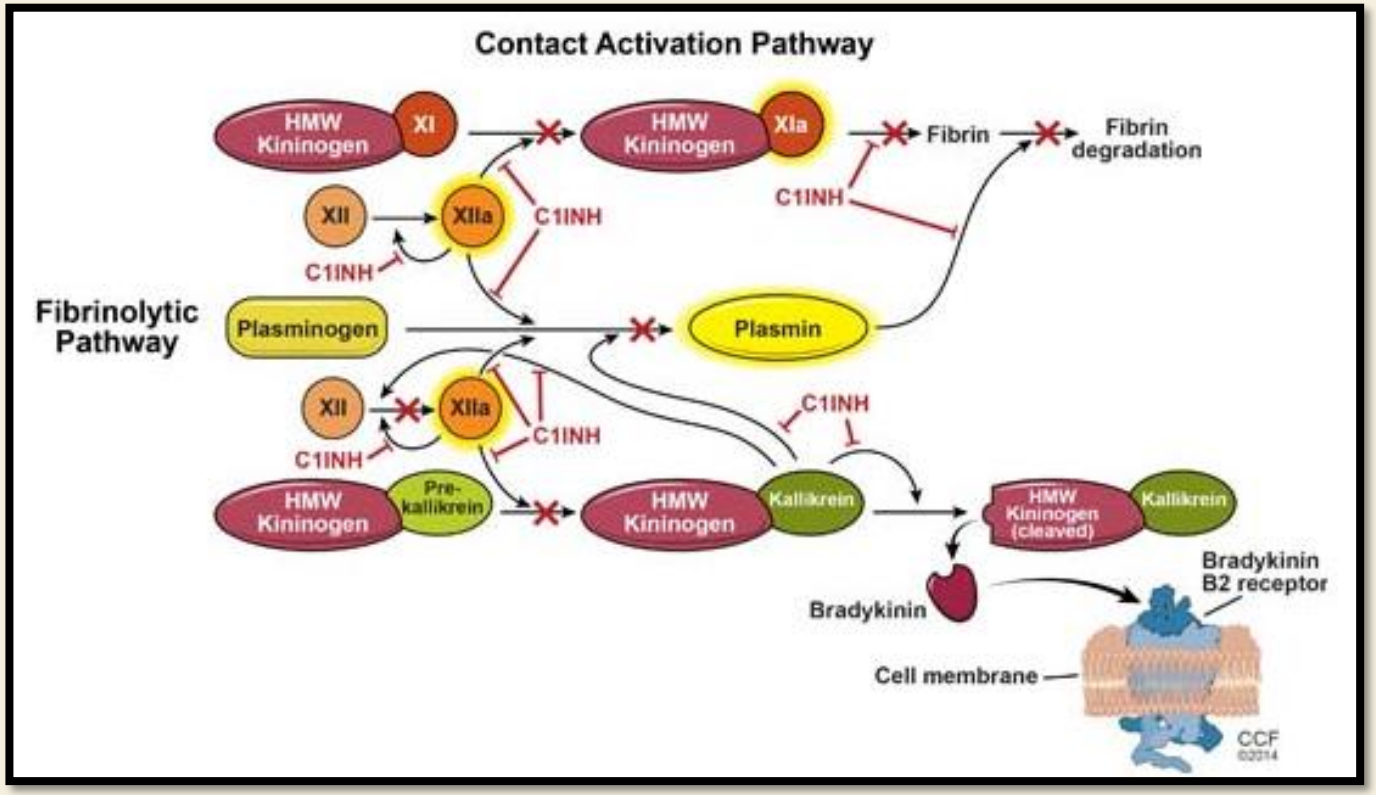


Sources: *Indian J Anaesth.* 2016; 60(8):534-41.

Dtsch Arztebl Int. 2017 Jul; 114(29-30): 489-96.

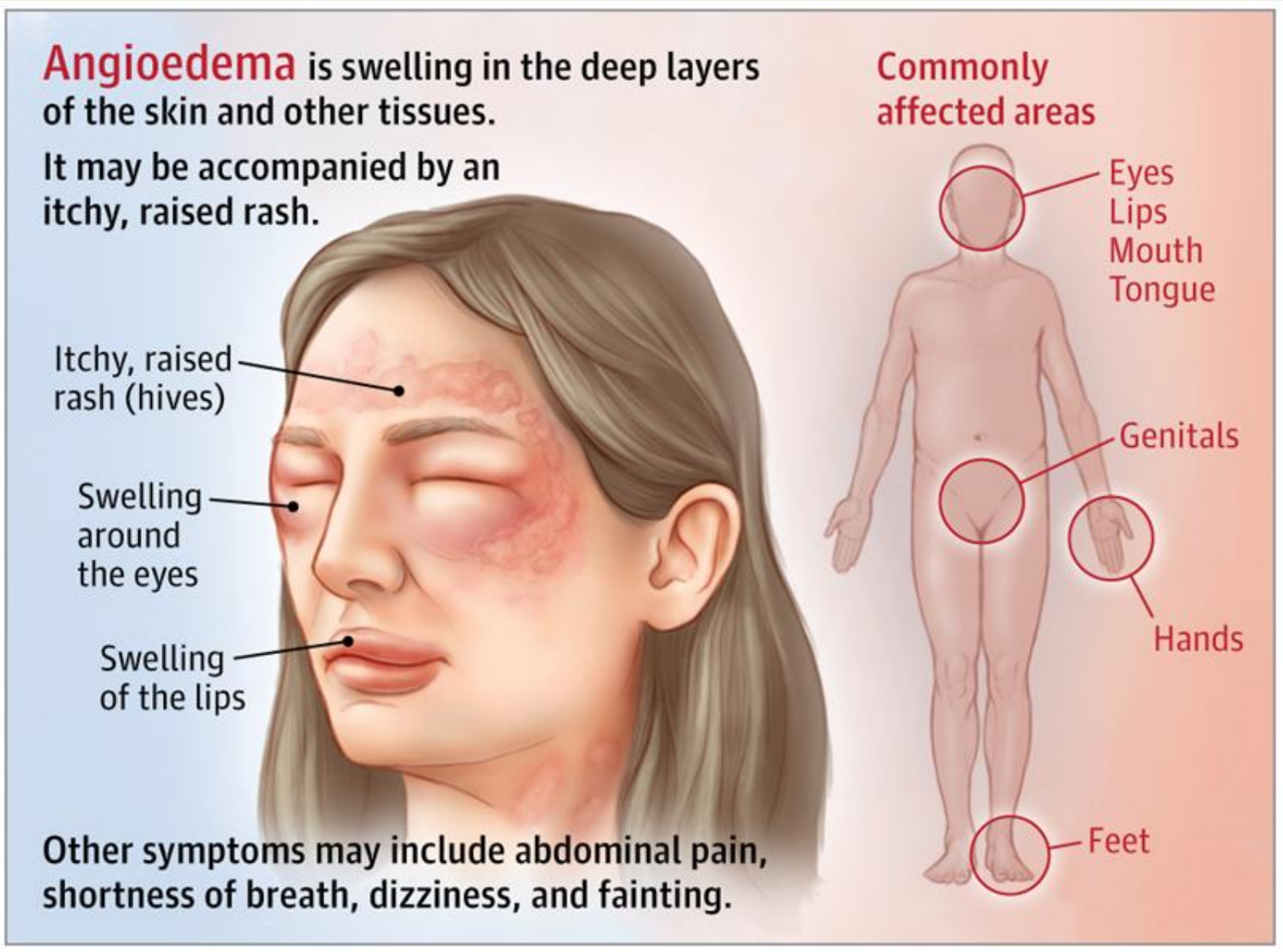
Bradykinin-Induced: Causes

- Hereditary Angioedema (HAE)
  - Genetic deficiency in C1 esterase inhibitor
- Acquired C1 esterase inhibitor deficiency
- Drugs
  - Angiotensin Converting Enzyme (ACE) inhibitors
  - Dipeptidyl peptidase-4 (DPP-4) inhibitors
  - Fibrinolytics: alteplase and streptokinase



Sources: *Acad Emerg Med.* 2014 Apr;21(4):469-84.
Figure 1. In: Hereditary angioedema. Cleveland Clinic Center for Continuing Education.

Presentation



Source: *JAMA*. 2018; 319(19):2054

Presentation

Mast-cell mediated

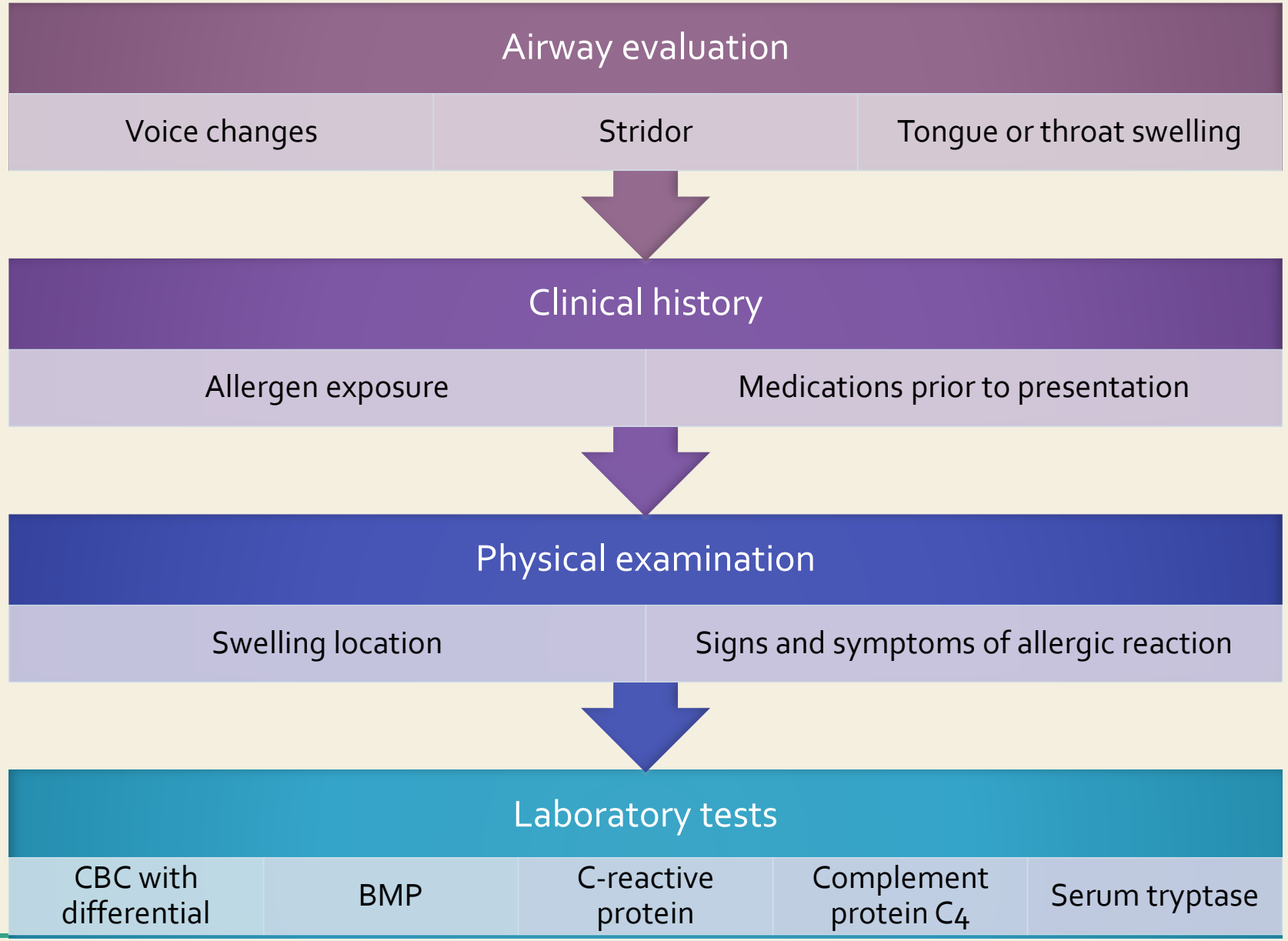
- Lips, tongue, laryngeal
- Immediate onset
- Symptoms may worsen over hours
- May include: urticaria, pruritus, bronchospasm, hypotension
- Resolution over 24 to 48 hours without treatment

Bradykinin-induced

- Lips, tongue, facial, abdominal, genitourinary
- Onset over hours to days
- Not associated with urticaria or bronchospasm
- Resolution over 3 to 5 days without treatment

Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.

Patient Work-up



Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.

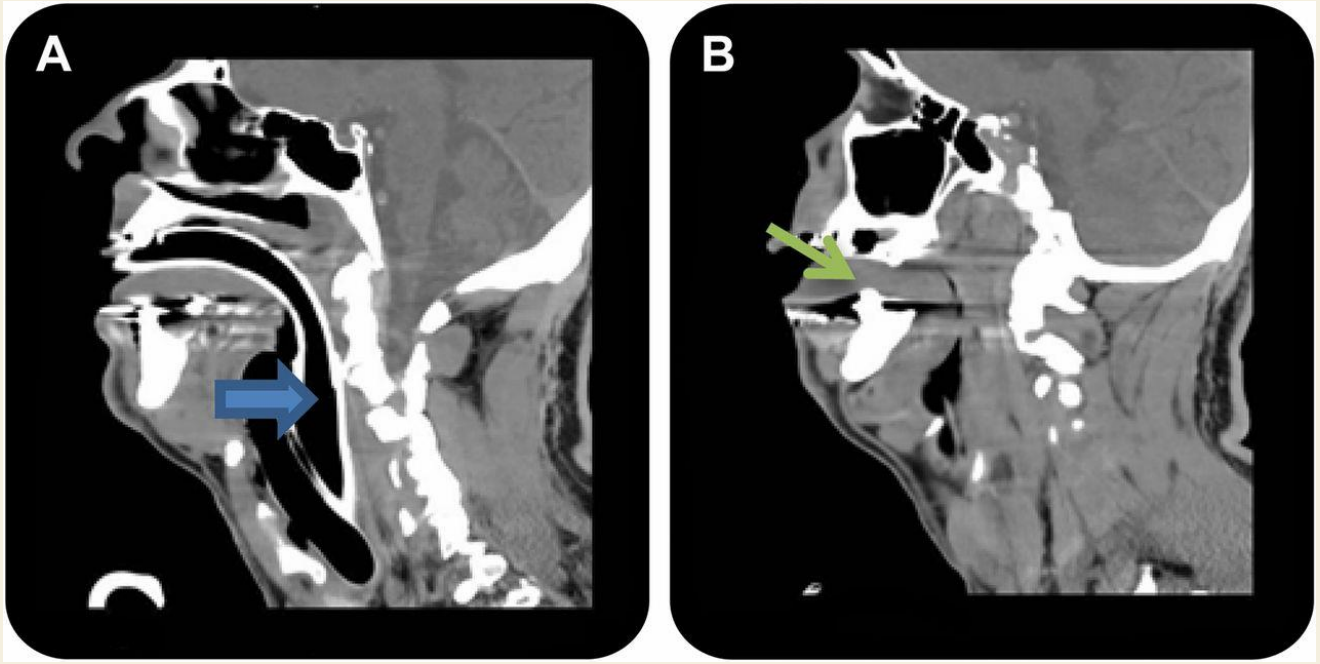
Diagnosis

- Angioedema is a clinical diagnosis based on physical findings and patient history
  - Determine the type of angioedema
- Differential diagnosis

Contact dermatitis	Cellulitis	Facial lymphedema
Autoimmune conditions	Eyelid edema	Parasitic infections
Hypothyroidism	Idiopathic edema	

Sources: *Allergy Asthma Proc*. 2002;23(5):337-88.
J Am Acad Dermatol. 2005;53(3):337-9.

Complications



- Compromise of the airway
  - Resultant hypoxia
  - Laryngeal angioedema can cause difficulty intubating
- Angioedema of the lips and mouth sometimes spreads to the throat
  - Frequent monitoring of patients

Sources: *Neurol Clin Pract*. 2012 Sept; 2(3):248-50.
Acad Emerg Med. 2014 Apr;21(4):469-84.

Knowledge Check 1: Patient Case

WG is a 56 YO AA male with a PMH of alcoholism, HTN, tobacco use and cocaine use who presented to the ED with symptoms suggestive of acute CVA (NIHSS of 6). Patient was treated with alteplase.

WG's home medications are as follows:

Albuterol	Aspirin	Disulfiram
Lisinopril	Pantoprazole	Sildenafil

One hour after completion of alteplase infusion, patient reports swelling of the right lower and upper lips. Angioedema is suspected.

Based on his presentation, what type of angioedema may WG be experiencing?

Knowledge Check 1

Based on his presentation, what type of angioedema is WG most likely experiencing?

A. Mast-cell mediated

B. Bradykinin-induced

C. WG is not experiencing angioedema

Knowledge Check 1, correct answer

Based on his presentation, what type of angioedema is WG most likely experiencing?

A. Mast-cell mediated

B. **Bradykinin-induced**

C. WG is not experiencing angioedema

Knowledge Check 2

What medication(s) may have contributed to WG developing angioedema? Select all that apply.

A. Lisinopril
B. Pantoprazole
C. Sildenafil
D. Alteplase
E. Aspirin

Knowledge Check 2, correct answer

What medication(s) may have contributed to WG developing angioedema? Select all that apply.

A. **Lisinopril**

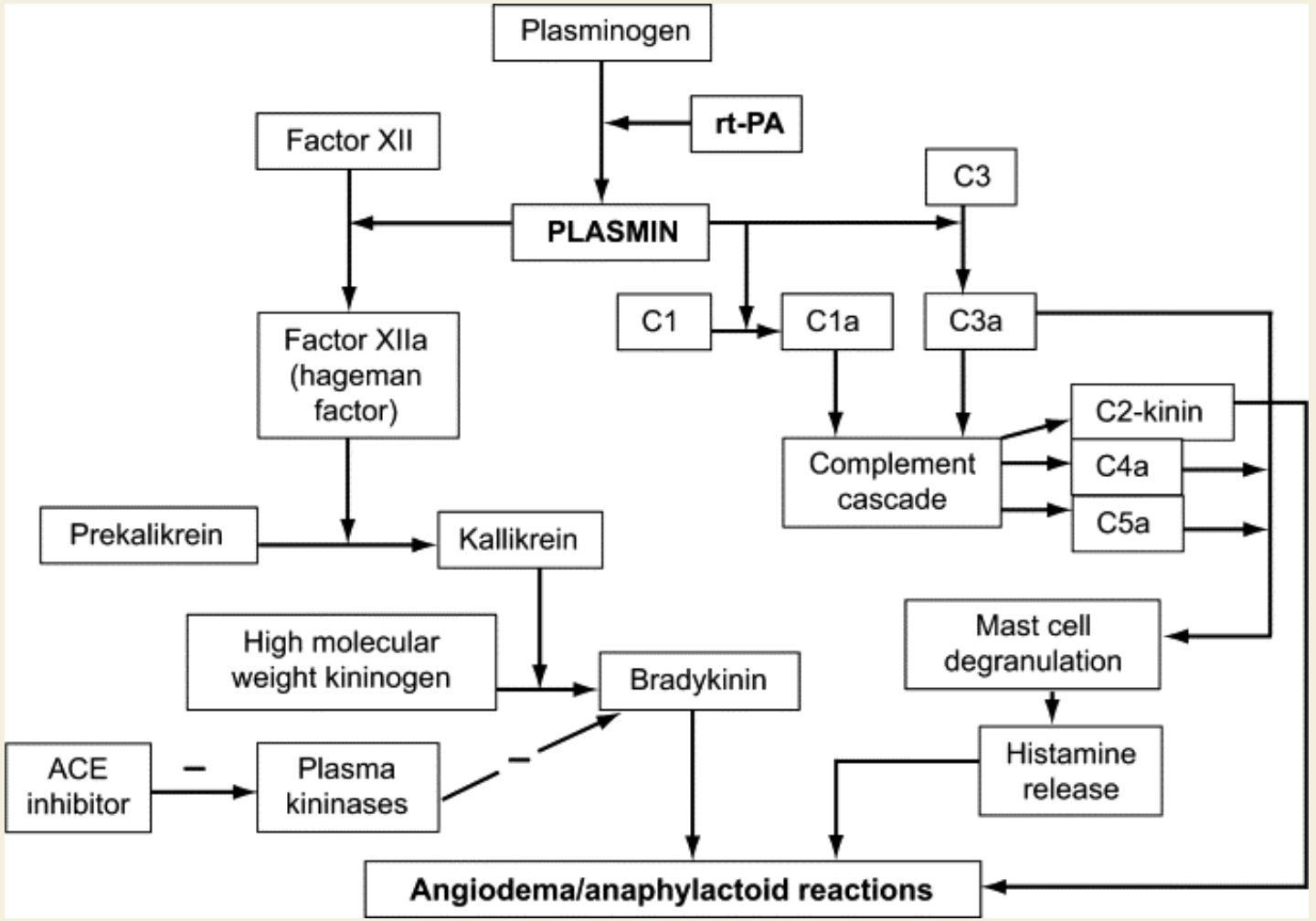
B. Pantoprazole

C. Sildenafil

D. **Alteplase**

E. **Aspirin**

Knowledge Check



Source: *Air Med J*. 2011;30(5):276-8.

ANGIOEDEMA TREATMENT

General Principles

Supportive Care

Monitor for airway compromise

When possible, identify type and cause of angioedema

Adjust treatment based on cause

Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.

Mast Cell-Mediated: Treatment

Epinephrine

- 0.3 or 0.5 mg IM x1
- May repeat every 5 to 15 minutes

Antihistamines

- H1 blockers: diphenhydramine 25 to 50 mg IV
- H2 blockers: famotidine 20 mg IV

Corticosteroids

- Methylprednisolone 1 to 2 mg/kg/day for 1 to 2 days
- May use equivalent dose of other corticosteroids

Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.
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Bradykinin-Induced: Treatment Options

Efficacy of treatment options depends on the underlying pathophysiology (i.e., drug-induced vs. hereditary)

- C1 esterase inhibitor
- Icatibant
- Ecallantide
- Fresh Frozen Plasma (FFP)
- Tranexamic Acid

Sources: *Acad Emerg Med.* 2014 Apr;21(4):469-84.
Rev Med Interne. 2018; 39(10):772-6.

C1 Esterase Inhibitor

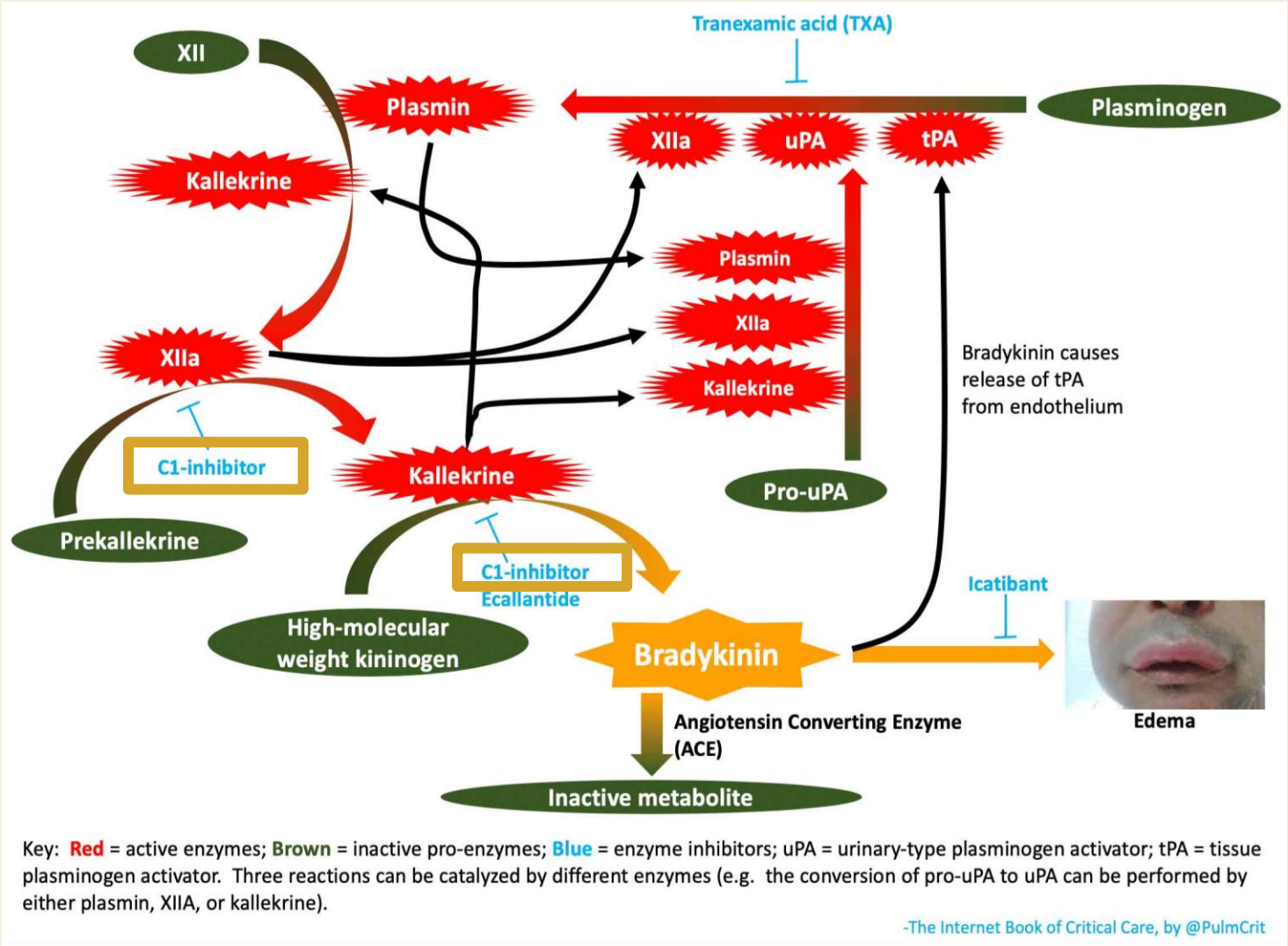
Berinert®, Cinryze®, Haegarda®, Ruconest®

Pharmacologic Category

- C1 esterase inhibitor

Mechanism of Action

- Inactivation of plasma kallikrein and factor XIIa, preventing bradykinin production



Key: **Red** = active enzymes; **Brown** = inactive pro-enzymes; **Blue** = enzyme inhibitors; uPA = urinary-type plasminogen activator; tPA = tissue plasminogen activator. Three reactions can be catalyzed by different enzymes (e.g. the conversion of pro-uPA to uPA can be performed by either plasmin, XIIA, or kallekrine).

-The Internet Book of Critical Care, by @PulmCrit

Source: Spiral activity which drives bradykinin-induced angioedema. The Internet Book of Critical Care. Lexi-Comp Online™

C1 Esterase Inhibitors

		Berinert®	Cinryze®	Haegarda®	Ruconest®
Formulation		Plasma-derived	Plasma-derived	Plasma-derived	Recombinant
FDA-approved Indications in HAE	Acute attack	Yes	No	No	Yes
	Prophylaxis	No	Yes	Yes	No
Route		IV	IV	SubQ	IV
Adult Dosing		20 IU/kg once	1000 units every 3 to 4 days	60 IU/kg every 3 to 4 days	50 units/kg once (max: 4,200 units)
Administration		IV: 4 mL/min May self-administer	IV: 1 mL/min May self-administer	Subcutaneous self-administration	IV: push over ~5 min May self-administer
Time to improvement		15 minutes	N/A	N/A	90 minutes
Approximate Price (AWP)		$3,720 (500 units)	$3,310 (500 units)	$2,323 (2000 units)	$7,480 (2100 units)

Source: Lexi-Comp Online™

C1 Esterase Inhibitors

Monitoring

- Hypersensitivity reactions
- Thrombotic events

HAE Attacks

- Place in Therapy: 1st line treatment
  - Berinert® and Ruconest® are the only C1 esterase inhibitors approved for the indication

ACE-I-induced Angioedema

- Efficacy
  - No studies examining the use
  - Case reports have indicated that it may be beneficial
- Place in Therapy: no evidence currently supporting use

Sources: *Allergy*. 208 Aug;73(8):1575-96.
Acad Emerg Med. 2014 Apr;21(4):469-84.
Lexi-Comp Online™

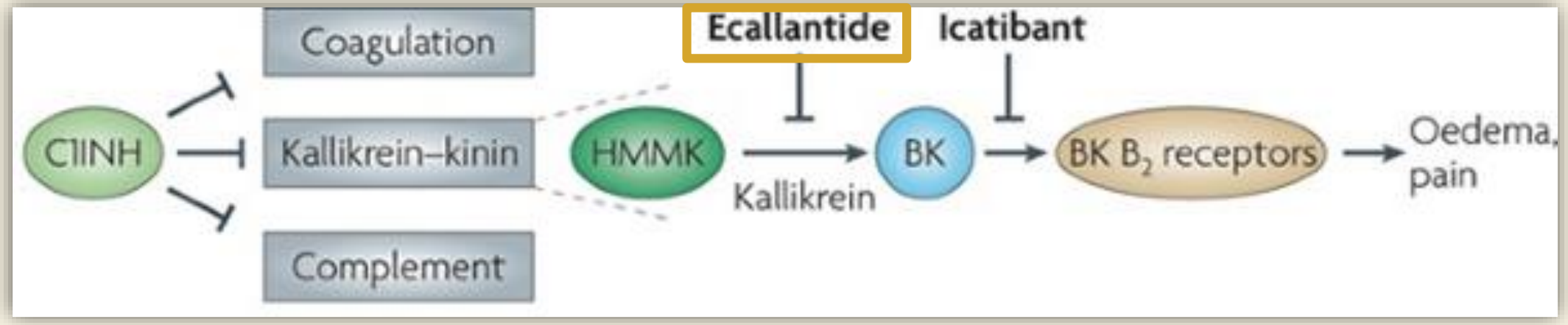
Ecallantide (Kalbitor®)

Pharmacologic Category

- Kallikrein inhibitor

Mechanism of Action

- Selectively inhibits plasma kallikrein, preventing the conversion of high molecular weight kininogen to bradykinin



Source: KALBITOR (ecallantide) [package insert]. Lexington, MA: Dyax Corp.; Revised Dec 2020.
Nat Rev Drug Discov. 2010; 9:189-90.

Ecallantide

FDA-approved Indications	Acute attack of HAE attack
Dosing	30 mg SubQ as three-10 mg (1 mL) injections May repeat within 24 hours
Administration	Administer subcutaneously in the abdomen, upper arm, or thigh (not at site of attack) Separate injections by at least 2 inches
Adverse Effects	Fatigue (12%), hypersensitivity reactions (4%), nausea and diarrhea
Price	Approximately $18,000 per dose (AWP)

Source: KALBITOR (ecallantide) [package insert]. Lexington, MA: Dyax Corp.; Revised Dec 2020.

Ecallantide

Hereditary Angioedema

- Efficacy: Sheffer et al.
  - Ecallantide significantly reduced Mean Symptom Complex Severity score and Treatment Outcome Score compared to placebo
- Place in Therapy: 1st line treatment

ACE-I Induced Angioedema

- Efficacy: Lewis et al. and Bernstein et al.

Study	Study Size	Primary Outcome	Ecallantide	Placebo	95% CI
Lewis et al.	76	ED discharge criteria met within 6 hours	87.9%	72.2%	-10.5 to 41.2 %
Bernstein et al.	50	ED discharge criteria met within 4 hours	31%	21%	-14 to 34%

- Place in Therapy: no clear place in therapy currently

Sources: *J Allergy Clin Immunol*. 2011 Jul;128(1):153-9.e4.
Ann Emerg Med. 2015 Feb;65(2):204-13.
Ann Allergy Asthma Immunol. 2015 Mar;114(3):245-9.

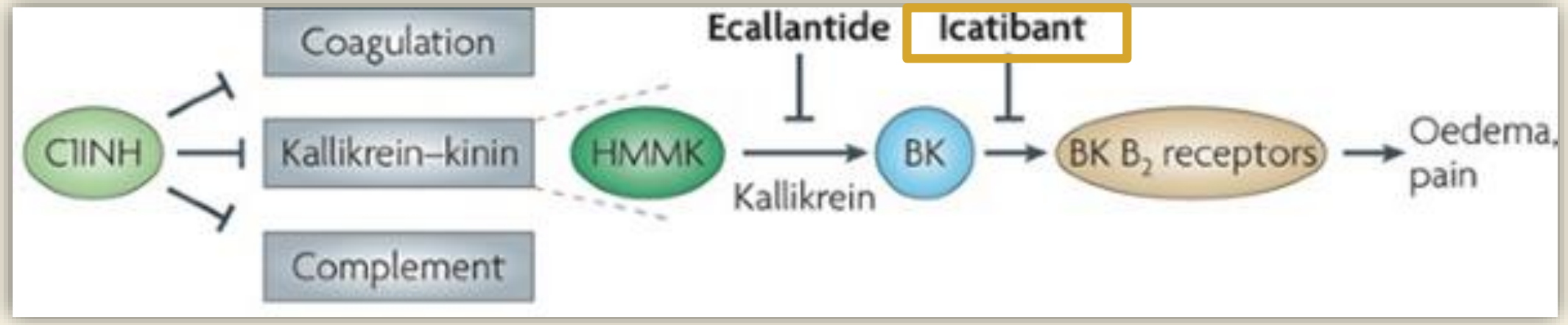
Icatibant (Firazyr®)

Pharmacologic Category

- Selective Bradykinin B2 Receptor Antagonist

Mechanism of Action

- Selective competitive antagonist for bradykinin B2 receptor
- Prevents the binding of bradykinin.



Sources: FIRAZYR (icatibant) [package insert]. Lexington, MA: Shire Orphan Therapies, Inc.; Revised Apr 2020. *Nat Rev Drug Discov*. 2010; 9:189-90.

Icatibant

FDA-approved Indications	Acute attacks of HAE
Dosing	30 mg SubQ May repeat every 6 hours
Administration Pearls	Administer 2 to 4 inches below belly button and away from any scars Do not administer in a painful or swollen area
Adverse Effects	Injection site reactions (97%), fever (4%), increased serum transaminases (4%)
Price	AWP: ~$4,500 per dose

Source: FIRAZYR (icatibant) [package insert]. Lexington, MA: Shire Orphan Therapies, Inc.; Revised Apr 2020.
Lexi-Comp Online™

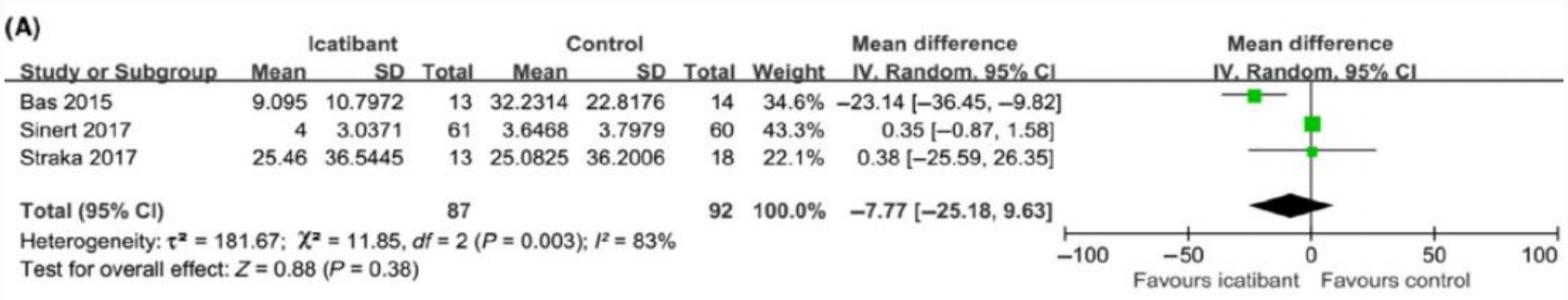
Icatibant

Hereditary Angioedema

- Efficacy: FAST-3 trial
  - Median time to 50% reduction in symptom severity was significantly shorter in icatibant compared to placebo (2 vs. 19.8 hours, p<0.001)
- Place in therapy: 1st line treatment

ACE-I Induced Angioedema

- Efficacy: Jinyoung J., et al.
  - Icatibant does not significantly improve the time to complete symptom resolution



- Place in Therapy: **not** recommended for the treatment of ACE-I-induced angioedema

Source: *Ann Allergy Asthma Immunol*. 2011 Dec;107(6):529-37.
J Clin Pharm Ther. 2019;44(5):685-92.

Fresh Frozen Plasma (FFP)

Mechanism of Action	Includes ACE → increases the breakdown of bradykinin Includes C1 esterase inhibitor → decreases the synthesis of bradykinin
Dosing	2 units of FFP
Monitoring	Transfusion reactions
Place in Acute Management	May be considered for refractory angioedema in both HAE and ACE-I induced

Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.
Blood products. The American Red Cross.

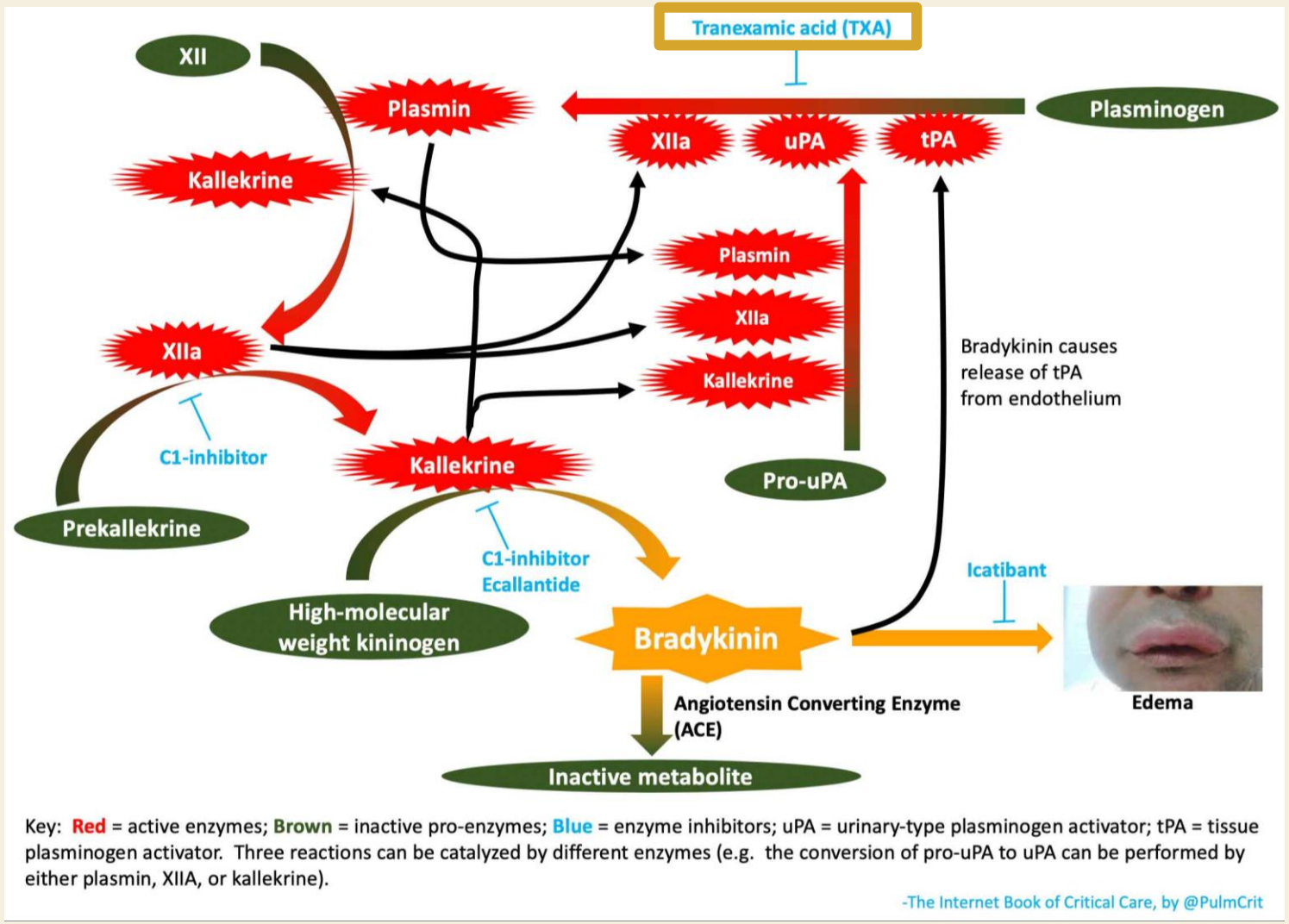
Tranexamic Acid

Pharmacologic Category

- Antifibrinolytic agent

Mechanism of Action

- Forms an irreversible complex with plasminogen, reducing plasma activity and reducing activation of C1 esterase inhibitor



Source: Spiral activity which drives bradykinin-induced angioedema. The Internet Book of Critical Care. Lexi-Comp Online™

Tranexamic Acid

Indication	Long-term prophylaxis for hereditary angioedema (off-label)
Dosing	Optimal dosing is unknown Doses of 0.5 to 4 gm IV or PO have been used
Monitoring	Hypersensitivity reactions, seizures, thrombotic events
Place in Acute Management	Proposed for treatment of ACE-I-induced angioedema – uncertain efficacy

Source: *Rev Med Interne*. 2018; 39(10):772-6.
Lexi-Comp Online™

Tranexamic Acid: Beauchêne et al

Design

- Retrospective analysis of 33 patients with severe bradykinin angioedema attributed to an ACE-I

Results

- 81.8% of patients had an adequate response to tranexamic acid alone
- The remaining patients required additional treatment with icatibant or a C1 esterase inhibitor
- No patients required intubation and there were no reported adverse effects

Conclusion

- Tranexamic acid may be an effective treatment for ACE-I-induced-angioedema but
- Additional studies are still needed to support its use

Source: *Rev Med Interne*. 2018; 39(10):772-6.

Knowledge Check 3

What is the mechanism of action of ecallantide?

A. Antifibrinolytic
B. ACE inhibitor
C. Kallikrein inhibitor
D. Selective Bradykinin B2 Receptor Antagonist

Knowledge Check 3, correct answer

What is the mechanism of action of ecallantide?

A. Antifibrinolytic

B. ACE inhibitor

C. Kallikrein inhibitor

D. Selective Bradykinin B2 Receptor Antagonist

HAE: Management

First-line

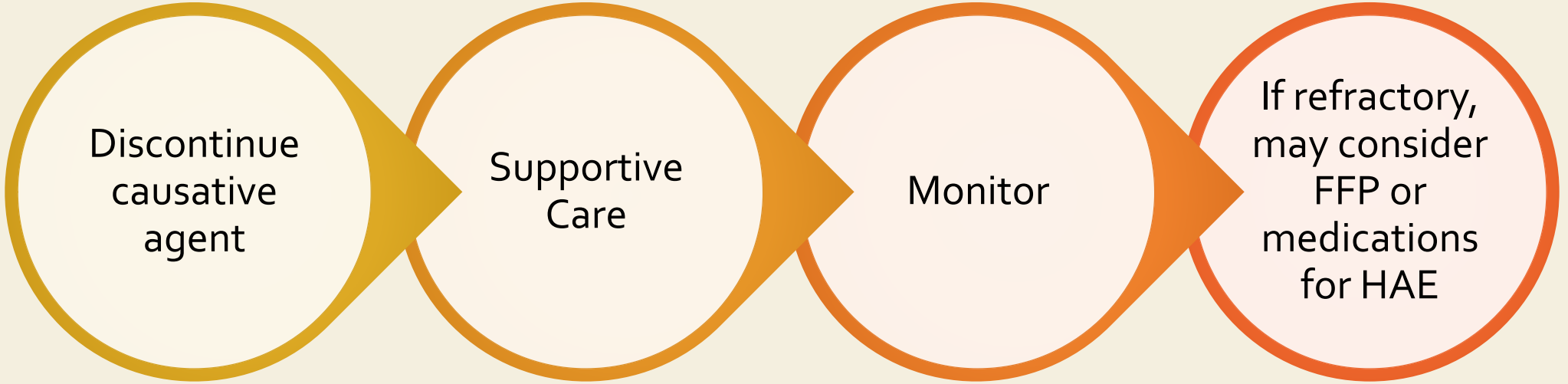
- C1 esterase inhibitor
- Icatibant
- Ecallantide

Second-line

- FFP

Source: *Allergy*. 208 Aug;73(8):1575-96.

ACE-I Induced: Management



Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.

Gaps in Knowledge

- Mechanism for drug-induced idiopathic angioedema
  - CCBs, ARBs, sirolimus, everolimus, amiodarone, metoprolol, risperidone, paroxetine
- Treatment of bradykinin-mediated drug-induced angioedema not caused by a C1 esterase inhibitor deficiency (hereditary or acquired)
  - ACE-inhibitors
  - DPP-4 inhibitors
  - Fibrinolytics
- Comparative efficacy of treatments for HAE

Knowledge Check 4: Patient Case

AL is a 28 YO female with a PMH of HTN and HAE presenting to the emergency department for abdominal pain and swelling in the lips and eyes. Her home medications include cetirizine and losartan. She currently has a patent airway. The physician is concerned about bradykinin-induced angioedema and asks for your recommendation.

Which of the following would you recommend for AL?

A. Diphenhydramine

B. Ecallantide

C. Epinephrine

D. Fresh Frozen Plasma

Knowledge Check 4, correct answer

AL is a 28 YO female with a PMH of HTN and HAE presenting to the emergency department for abdominal pain and swelling in the lips and eyes. Her home medications include cetirizine and losartan. She currently has a patent airway. The physician is concerned about bradykinin-induced angioedema and asks for your recommendation.

Which of the following would you recommend for AL?

A. Diphenhydramine

B. Ecallantide

C. Epinephrine

D. Fresh Frozen Plasma

Summary: Types of Angioedema

Mast-Cell Mediated	Bradykinin-induced
Rapid onset	Insidious onset
Possible urticaria	No urticaria
Resolves over 24-48 hours	Resolves over 3-5 days
Allergic, pseudo-allergic, NSAIDs, fibrinolytics	HAE, acquired C1 esterase inhibitor deficiency, ACE-I, DPP-4 inhibitors, fibrinolytics
Treated with epinephrine, antihistamines and corticosteroids	Treatment varies based on cause

Source: *Acad Emerg Med.* 2014 Apr;21(4):469-84.

Summary

- Angioedema is swelling of the subcutaneous tissue
  - Depending on severity, angioedema can be a medical emergency
- There are two main types of angioedema: mast-cell mediated and bradykinin-mediated.
- Treatment should be narrowed based on the cause
  - Mast-cell mediated angioedema should be treated with epinephrine, antihistamines and corticosteroids
  - Hereditary angioedema attacks can be treated with C1 esterase inhibitors, selective bradykinin B2 receptor antagonist, kallikrein inhibitor and fresh frozen plasma
  - The treatment of bradykinin-induced angioedema caused by medications involves the discontinuation of the causative agent and supportive care.

References

Beauchêne C, Martins-Hericher JM, Denis D, et al. Tranexamic acid as first-line emergency treatment for episodes of bradykinin-mediated angioedema induced by ACE inhibitors. *Rev Med Interne*. 2018; 39(10):772-6.

Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133(5):e1-66.

Bernstein JA, Moellman JJ, Collins SP, et al. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor-induced angioedema in the emergency department. *Ann Allergy Asthma Immunol*. 2015 Mar;114(3):245-9.

Blood products. The American National Red Cross. Accessed January 1, 2021. <https://www.redcrossblood.org/biomedical-services/hospital-customers/blood-products-andservices.html>

Charlesworth EN. Differential diagnosis of angioedema. *Allergy Asthma Proc*. 2002;23(5):337-88.

da Silva IRF, Liberato BB. Airway management in a patient with severe angioedema after thrombolysis for ischemic stroke. *Neurol Clin Pract*. 2012 Sept; 2(3):248-50.

Delves PJ. Angioedema. In: Merck Manuals Professional Edition. [Internet] Kenilworth, NJ: Merck Manuals; 2021 [cited 12 Jan 2021]. <https://www.merckmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/angioedema?query=angioedema>

Farkas J. Spiral activity which drives bradykinin-induced angioedema. The Internet Book of Critical Care. Published August 1, 2019. Accessed January 14, 2021. <https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/hereditary-angioedema/>

FIRAZYR (icatibant) [package insert]. Lexington, MA: Shire Orphan Therapies, Inc.; Revised Apr 2020.

Hahn J, Hoffmann TK, Bock B, et al. Angioedema: an interdisciplinary emergency. *Dtsch Arztebl Int*. 2017 Jul; 114(29-30): 489-96.

Jinyoung J, Lee YJ, Lee SY. Effect of icatibant on angiotensin-converting enzyme-induced angioedema: a meta analysis of randomized controlled trials. *J Clin Pharm Ther*. 2019;44(5):685-92.

References

KALBITOR (ecallantide) [package insert]. Lexington, MA: Dyax Corp.; Revised Dec 2020.

Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol*. 2005;53(3):337-9.

Lewis LM, Graffeo C, Crosley P, et al. Ecallantide for the acute treatment of angiotensin-converting enzyme inhibitor-induced angioedema: a multicenter, randomized, controlled trial. *Ann Emerg Med*. 2015 Feb;65(2):204-13.

Lexi-Comp Online™, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; Updated periodically.

Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol*. 2011 Dec;107(6):529-37.

Maertins M, Wold R, Swider M. Angioedema after administration of tPA for ischemic stroke: case report. *Air Med J*. 2011;30(5):276-8.

Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 208 Aug;73(8):1575-96.

Misra L, Khurmi N, Trentman TL. Angioedema: Classification, management and emerging therapies for the perioperative physician. *Indian J Anaesth.* 2016; 60(8):534-41.

Moellman JJ, Bernstein JA, Lindsell C, et al. A consensus parameter for the evaluation and management of angioedema in the emergency department. *Acad Emerg Med.* 2014 Apr;21(4):469-84.

Sheffer AL, Campion M, Levy RJ, et al. Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol*. 2011 Jul;128(1):153-9.e4.

Siles Roxana. Figure 1. In: Hereditary angioedema. Cleveland Clinic Center for Continuing Education. Published April 2017. Accessed January 14, 2021. <https://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/allergy/hereditary-angioedema/>

Tarbox JA, Bansal A, Peiris AN. Angioedema. *JAMA*. 2018; 319(19):2054

Zuraw B, Yasothan U, Kirkpatrick P. Ecallantide. *Nat Rev Drug Discov*. 2010; 9:189-90.

Thank you!

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