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Clinical Meeting & Exhibition

Read My Lips: A Case-Based Approach to Managing Acute Angioedema

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Objectives

- Review current causes and treatments for patients presenting with general angioedema.
- Evaluate treatment for patients who present with acute hereditary angioedema.
- Select treatment for patients who present with angiotensin-converting enzyme inhibitor angioedema.

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Don’t Take My Breath Away: Recognizing and Treating the Acute Angioedema Patient

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Patient Case 1

45 yo AAM arrives in your ED with a complaint of tongue and lip swelling he noticed when brushing his teeth. Patient denies any medical conditions, allergies, previous angioedema events, or events in his family. Patient's wife states he was at the beach all day & ate at a new Thai restaurant.

Which type of angioedema might he be presenting with?

Patient Case 1

A. Immunologic/Allergy
B. Hereditary
C. ACE-Inhibitor Induced
D. Physically Induced

Angioedema

- 80,000-120,000 ED visits annually
  - ~18% are hospitalized
- May coexist with urticarial
- Enhanced vascular permeability results in subcutaneous or submucosal tissue swelling
- Skin appears normal
  - Non-pitting
  - Non-pruritic
- Commonly affects lips, tongue & eyelids

Moellman JJ, et al. *Acad Emerg Med*. 2014 April;21(4):469–484.

Classification of Angioedema

Immunological/Allergic	• IgE mediated reaction
Hereditary	• Deficiency in quantity or functionality of C1-INH due to genetic defect
Acquired	• Deficiency in quantity or functionality of C1-INH not due to genetic defect
ACE-Inhibitor Induced	• Adverse reaction to a medication
Physically Induced	• Extremes of temperature, physical activity, UV radiation or vibration
Idiopathic	• Unknown etiology with multiple attacks

Wilkerson GR. *EM Pract*. 2012 Nov;14(11).


STEP 1: STABILIZE

Stabilization

- Vitals
- Airway assessmet
- O_2 status
- ECG monitoring
- Prepare for intubation
- Placement in area for frequent assessment

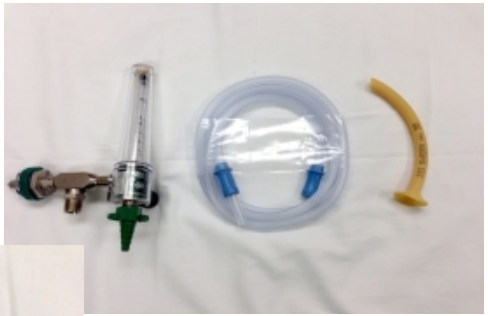
Ishoo Staging of Angioedema

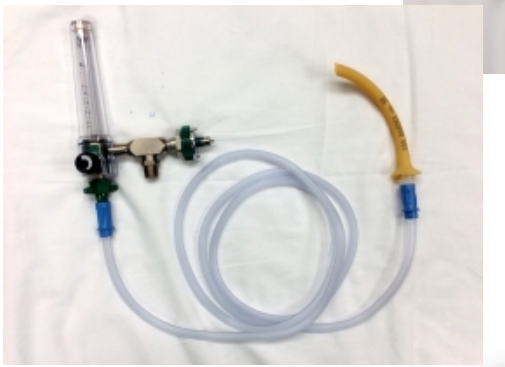
Stage	Site	Episodes (%)	Outpatient Tx (%)	Floor Tx (%)	ICU Tx (%)	Intervention (%)
I	Face, lip	31	48	52	0	0
II	Soft palate	5	60	40	0	0
III	Tongue	32	26	7	67	7
IV	Larynx	31	0	0	100	24

Ishoo E, et al. Otolaryngology – Head Neck Surg. 1999;121(3)265.

Tools for Oxygenation

- Flexible fiber optic laryngoscopy
- Laryngeal mask
- Nasopharyndeal oxygenation

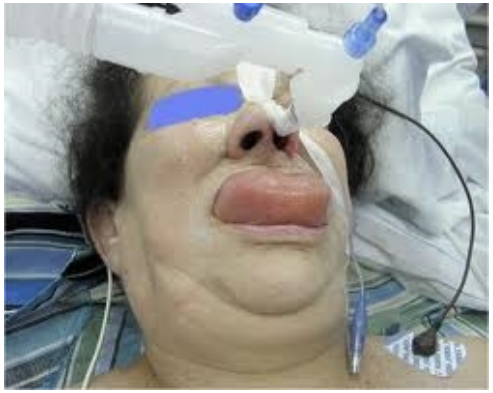




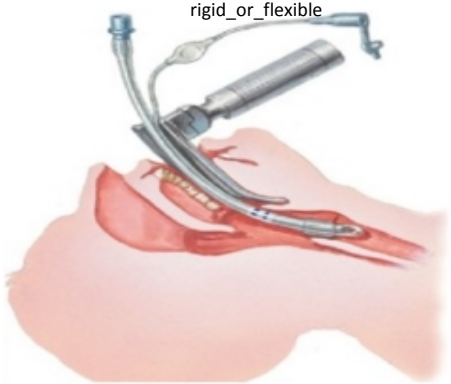
https://www.aliem.com/2014/03/trick-trade-nasopharyngeal-oxygenation

Monitoring and Intubation

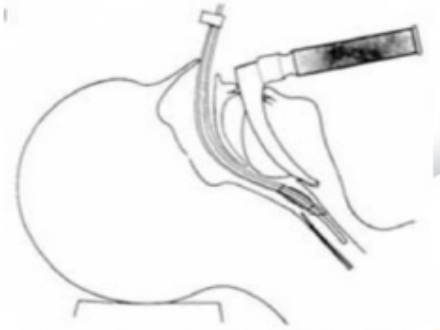
- Monitoring
  - General respiratory management
  - To intubate or not to intubate?
- Intubation
  - Nasal vs. oral intubation
  - Fiberoptic
  - Cricothyrotomy



http://www.aschoolofairway.com/airway_devices/fiberoptics_rigid_or_flexible



Orotracheal Intubation



Nasotracheal Intubation

Acad Emerg Med. 2014 April ; 21(4): 469–484.

http://image.slidesharecdn.com/advancedairwaymanagement-111229140903-phpapp02/95/advanced-airway-management-22-728.jpg?cb=1325169055


STEP 2: DIFFERENTIATE
STEP 1: STABILIZE

Differential Diagnosis

- Classes of angioedema +/- urticaria
- Anaphylaxis
- Edema
- Dermatitis
- Cellulitis
- Muckle-Wells syndrome
- Venous obstructive diseases
- Gleich syndrome
- Ascher syndrome
- Melkersson-Rosenthal syndrome
- Filariasis

Wilkerson GR. *EM Pract*. 2012 Nov;14(11).

History & Physical

- Prior attacks
- Family history (hereditary)
- Medical history
- Current medications
- Allergies & triggers
- Symptoms
- Onset & progression
- Edema location
- Laboratory findings
  - C1-INH levels
  - C4 levels


STEP 3: TREATMENT
STEP 2: DIFFERENTIATE
STEP 1: STABILIZE

Patient Case 2

You provider would like to intubate the patient at this time due to wheezing and angioedema, but the patient is very concerned and would like to see if anything else can be done prior.

Which medication would you recommend as the first medication?

Patient Case 2

A. Epinephrine 0.3 mg IV
B. Prednisone 60 mg PO
C. Epinephrine 0.3 mg IM
D. Diphenhydramine 25 mg IV

Treatment Options

- Is there evidence of anaphylaxis?
- What type of angioedema are you dealing with?
- What other medications is the patient on?
- If I'm not sure – I go with empiric treatment!

Epinephrine

- First-line in patients with respiratory distress, severe laryngeal edema or anaphylaxis
- Dosing:
  - 0.3 mg (0.2-0.5 mg) IM q15-20 minutes
  - 0.01 mg/kg (max of 0.3 mg)
- IM better than SQ in studies
- Lateral thigh superior to deltoid
  - Only need 60 mmHg to absorb
- Use 1 mg/mL concentration

  **Note: labeling changed to only reflect mg/mL (no more 1:1,000 vs 1:10,000 – Yay!!!)

Simons, et al. *J Allergy Clin Immunol*. 2001;108:871-873.
Simons, et al. *J Allergy Clin Immunol*. 1998;101:33-37

Epinephrine IV

- Reserved for patients in cardiac arrest or receiving multiple IM doses commonly
- Must dilute!!!!!
- Dosing:
  - 1-4 mcg/min
  - Consider starting lower – beta activity

Glucagon

- May consider in patients taking beta-blockers
  - May have decreased response to epinephrine
- Glucagon affects cAMP independently of beta-receptor
- Dosing:
  - 1-5 mg IV over 5 min
  - 20-30 mcg/kg IV (max of 1 mg) in pediatrics
  - Infusion: 5-15 mcg/min

Sampson HA, et al. Ann Emerg Med. 2006;47(4)373-380.

Histamine Antagonists

Second-line in anaphylaxis situations

- H1 Antagonist
  - Guidelines suggest second generation
    - Limitations in formulation and availability
  - Diphenhydramine most commonly use as IV
- H2 Antagonists
  - 15% of histamine receptors in skin are H2

Dibbern, D.A., et al. *Immunol Allergy Clin North Am.* 2004.24(2):141-62.
Kanani, et al. *Allergy, Asthma & Clinical Immunology. 2011.7(suppl 1):59*

Corticosteroids

- Inhibits T helper cells & inflammatory mediators
- Second line agent
  - Delayed effect
  - May prevent rebound or longer reaction
- No high-quality data to show efficacy in angioedema

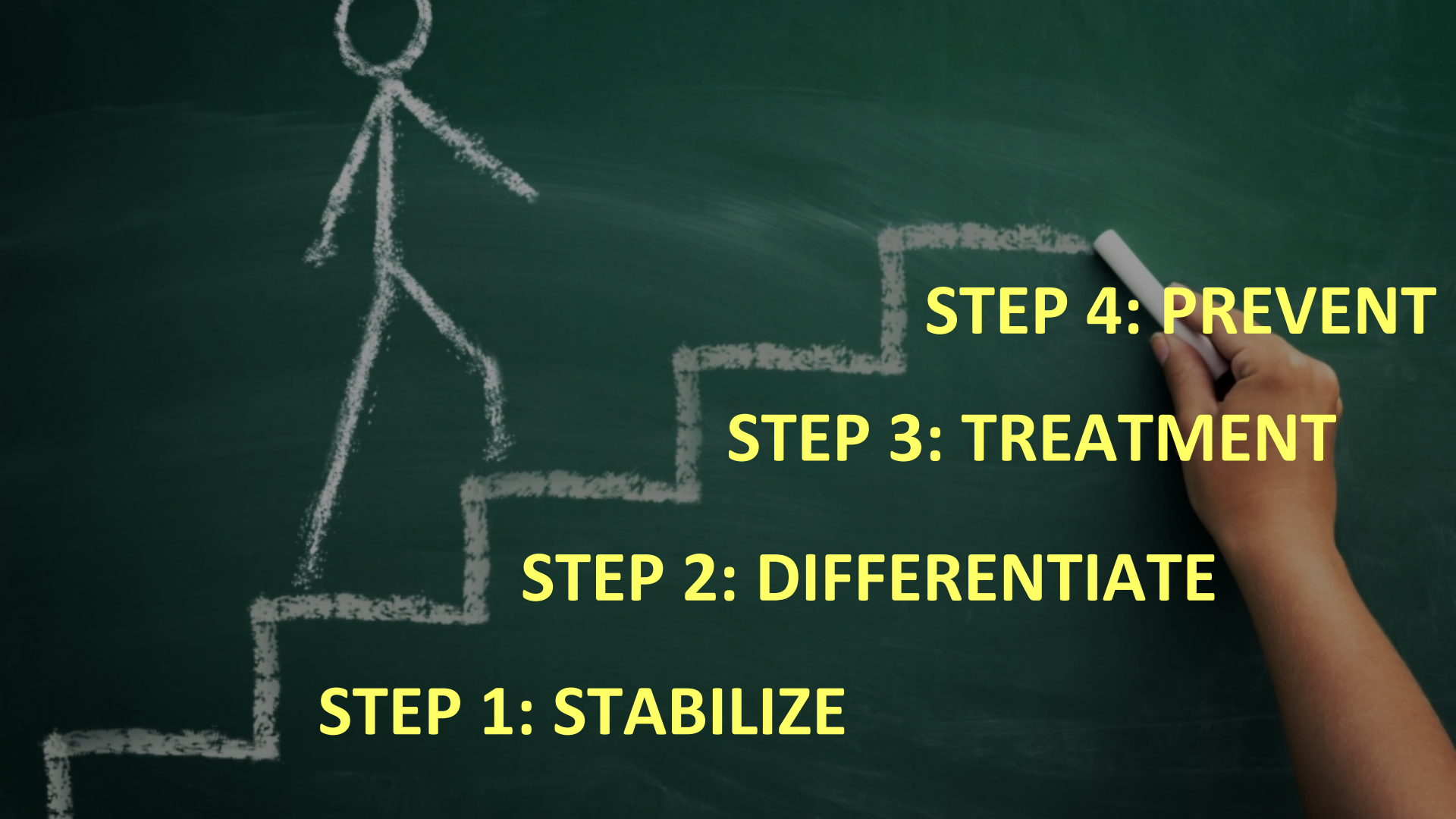
Wilkerson GR. *EM Pract*. 2012 Nov;14(11).

Biphasic Reactions

- Potential for 2nd episode up to 8hr after

- Only 5 of 496 anaphylaxis visits had
  - 2 within ED visit
  - 3 after discharge
  - No deaths
- Probably don't need long observation

Grunau BE, et al. Ann Emerg Med. 2014 June;63(6):736-744.


STEP 4: PREVENT
STEP 3: TREATMENT
STEP 2: DIFFERENTIATE
STEP 1: STABILIZE

Prevention

- Remove offending allergen (if identified)
- Send patient home with self-administered epinephrine!!!!
  - Epi-pen (0.3 mg IM)
  - Epi-pen JR (0.15 mg IM)
- Education on use
- If possible fill/dispense prior to leaving ED

Key Takeaways

- Key Takeaway #1
  - Differentiation of types of angioedema are key to selecting therapeutic options. If unknown, empiric therapies should be started after stabilization.
- Key Takeaway #2
  - Epinephrine IM is the first-line agent for all patients with respiratory distress, severe laryngeal edema or anaphylaxis
- Key Takeaway #3
  - All patients should receive a self-administration epinephrine device

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Swelling That's Not Swell: Managing Acute Hereditary Angioedema

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Patient Case Part 1

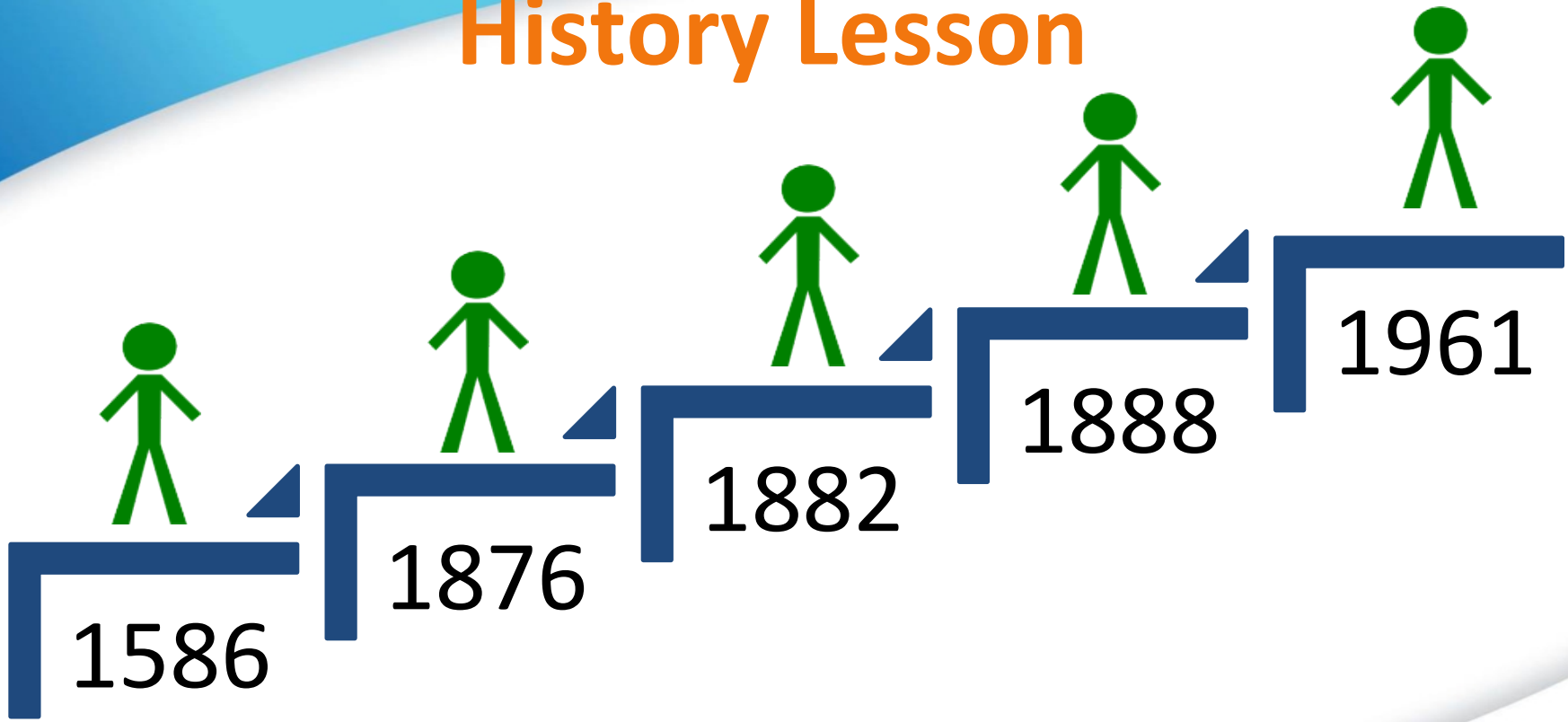
TY is a 17-year-old female with no known PMH that presents with face and neck swelling and laryngeal edema. Patient denies any known food or medication allergies. Patient is unable to report any family history of angioedema and other family members are not available at this time.

Which of the following would be the most appropriate empiric treatment option based on symptoms?

Patient Case cont.

A. Icatibant
B. C1INH (Berinert®)
C. Epinephrine, methylprednisolone, and diphenhydramine
D. Ecallantide

History Lesson



Khan DA. *Allerg Asthma Proc* 2011;51:doi: 10.2500/aap.2011.32.3411.

Hereditary Angioedema (HAE)

- Rare, autosomal-dominant disorder
- Manifests in childhood and associated with high morbidity but low mortality
- Three types of HAE:
  - Type I – deficiency of C1 esterase inhibitors (80-85%)
  - Type II- malfunction of C1 esterase inhibitors (20-25%)
  - Type III- normal C1 esterase activity (rare)

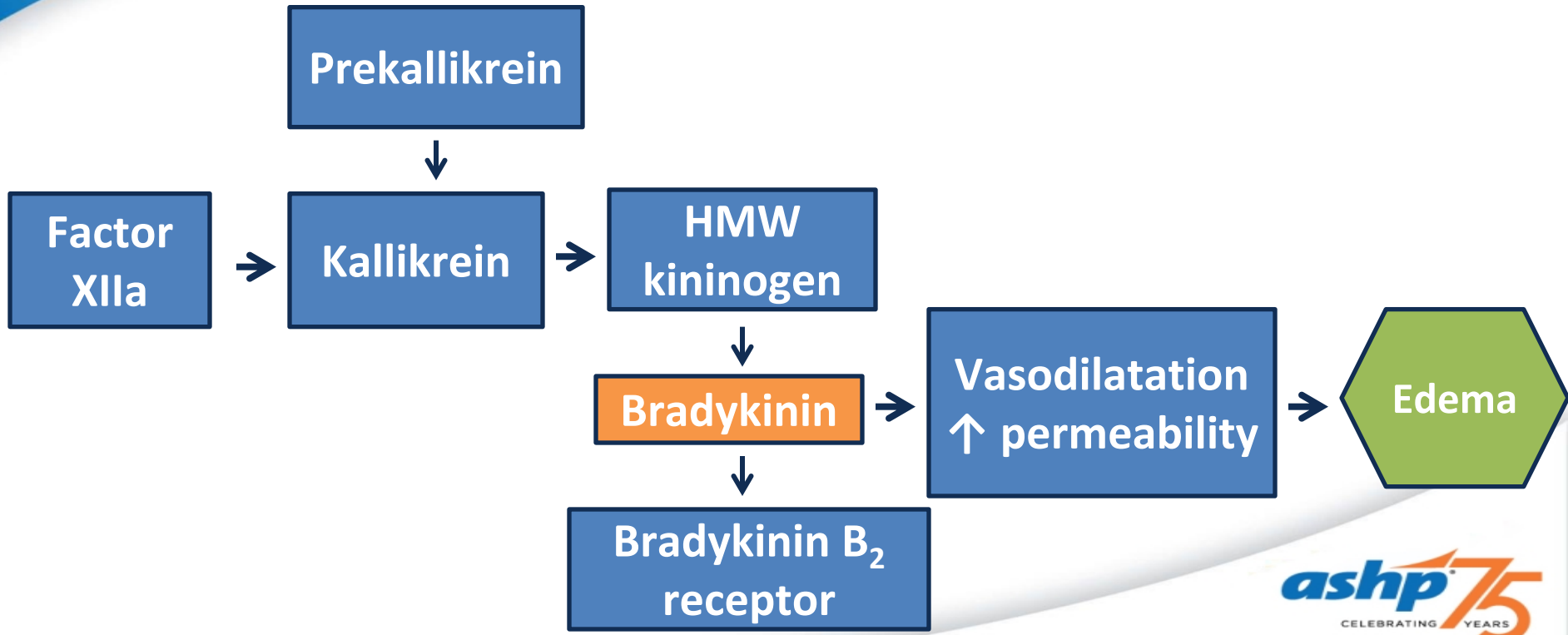
Zuraw BL, et al. *Clinic Rev Allerg Immunol* 2016;51:216-229.

HAE Diagnosis

- Clinical criteria is usually first sign
  - Recurrent non-pruritic edema
  - Family history
- Diagnosis of exclusion
- Laboratory studies:
  - ↓ C1 esterase inhibitor concentrations
  - Improper C1 esterase inhibitor activity
  - Abnormal genetic markers

Zuraw BL, et al. *Clinic Rev Allerg Immunol* 2016;51:216-229.
Zuraw BL, et al. *J Allergy Clin Immunol* 2013;131:1491-3.

Pathogenesis



Patient Case Part 2

TY's mother has arrived to the ED. She states that there is history of HAE in the family. Patient has increased laryngeal edema and is unable to protect her airway.

Which of the following would be the most appropriate treatment option based on symptoms?

Patient Case Cont.

A. Ecallantide
B. C1INH (Berinert®)
C. Fresh frozen plasma
D. Intubation/supportive care measures

Acute Treatment of HAE

- Empiric treatment for unknown diagnosis:
  - Epinephrine, antihistamines and corticosteroids
  - Usually not efficacious but leads to HAE diagnosis
- Secure airway/supportive care
  - Intubation if laryngeal edema
- C1 inhibitor therapy, icatibant, or ecallantide
  - Based on swelling location and availability

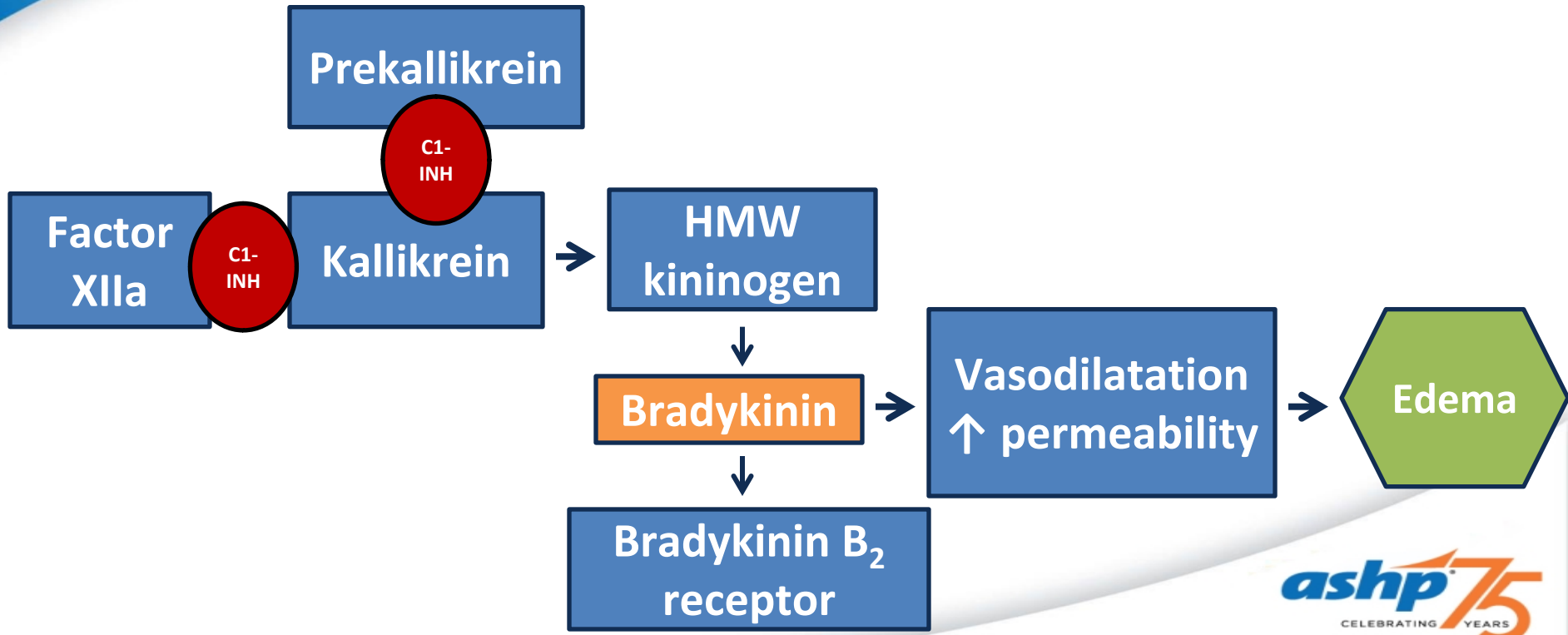
Bowen T, et al. *Allergy Asthma Clin Immunol* 2010;6:24.

HAE Treatment

- Goals of treatment:
  - Avoidance of swelling
  - Reduction of attack frequency and severity
- Available treatment targets:
  - Replacement of C1INH
  - Bradykinin B_2 receptor blocker
  - Plasma kallikrein inhibitor
  - Increase concentrations of C4 complement
  - Inhibition of plasminogen

Zuraw BL, et al. *Clinic Rev Allerg Immunol* 2016;51:216-229.
Zuraw BL, et al. *J Allergy Clin Immunol* 2013;131:1491-3.

C1INH therapy



C1INH Concentrates

(Berinert®/ Cinryze®)

- C1INH Replacement
- Clinical trials have shown significantly faster symptom resolution during acute treatment
- Median onset is 30-60 mins
- Must be brought to room temperature and reconstituted prior to administration
- Preferred treatment in children < 12 yrs of age and pregnancy

Bork K, et al. *Arch Intern Med* 2001;161:714-8.
Craig TJ, et al. *J Allergy Clin Immunol* 2009;124:801-8.
Craig TJ, et al. *J Clin Immunol* 2010;30:823-9.
Zuraw BL, et al. *N Engl J Med* 2010;363:513-22.

Conestat alfa

- Recombinant human C1INH
- Trials have shown that administration was safe and more effective then placebo in reducing HAE symptoms
- Contraindicated in patients with allergy to rabbits or rabbit-derived products
- Must be brought to room temperature and reconstituted prior to administration

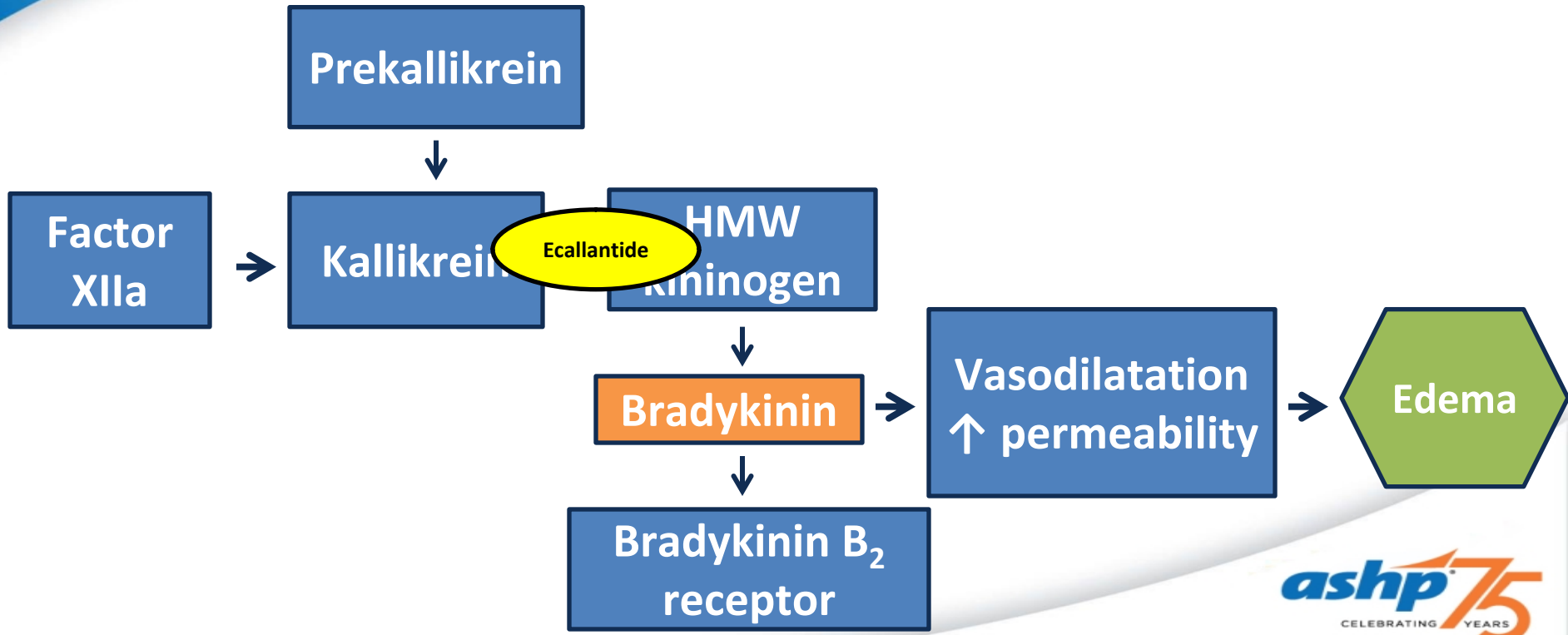
Zuraw BL, et al. *N Engl J Med* 2010;363:513-22.
Riedl MA, et al. *Ann Allergy Asthma Immunol* 2014;112:163-9.

Fresh Frozen Plasma (FFP)

- C1INH replacement
- Considered 2nd line to the other C1INH therapies
  - No head to head trial comparing C1INH therapies to FFP
- Monitor volume overload
- Long thaw time and potential for transfusion-associated adverse outcomes

Prematta M, et al. *Ann Allergy Asthma Immunol* 2007;98:383-8.

Ecallantide

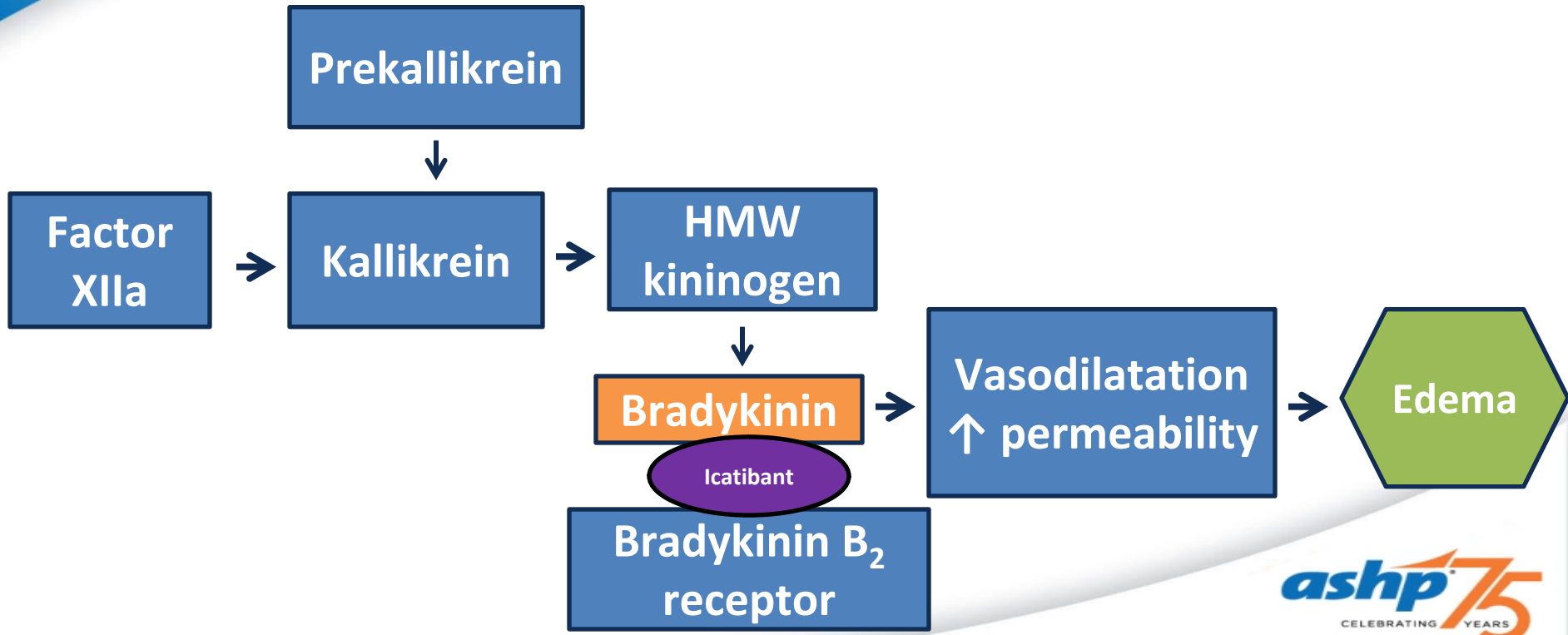


Ecallantide

- EDEMA3:
  - Improvement in patient reported treatment scores (p=0.004)
  - No difference in time to significant improvement (p=0.14)
- EDEMA4:
  - Greater change in severity score from baseline (p=.01) and treatment score (p=0.003)
- Black Box Warning:
  - Risk of possible anaphylaxis and should be administered in a controlled setting

Cicardi M, et al. *N Engl J Med* 2010b;363:523-31.
Levy RJ, et al. *Ann Allergy Asthma Immunol* 2010;104:523-9.

Icatibant


Prekallikrein
Factor XIIa
Kallikrein
HMW kininogen
Bradykinin
Icatibant
Bradykinin B_2 receptor
Vasodilatation ↑ permeability
Edema

Icatibant

- FAST-1: Placebo vs. icatibant
  - Median time to clinically significant relief: 2.5 hrs icatibant vs. 4.6 hours placebo, p=0.14
- FAST-2: Oral TXA vs. icatibant
  - Median time to clinically significant relief: 2 hrs icatibant vs. 12 hours TXA, p<0.001
- FAST-3: Placebo vs. icatibant
  - Decreased time to symptom relief in cutaneous, abdominal and laryngeal HAE, p<0.001
- Caution use in patients with ischemic heart disease
  - Blockage of B2 receptor ↓ coronary blood flow

Cicardi M, et al. *N Engl J Med* 2010;363:532-41.
Lumry WR, et al. *Ann Allergy Asthma Immunol* 2011;107:529-37.

Patient Case Part 3

TY has now been intubated, stabilized, and supportive care measures have been started. The physician would like to start a pharmacological agent for the treatment of HAE.

Which of the following would be the most appropriate treatment option?

Patient Case Cont.

A. Ecallantide
B. Icatibant
C. C1INH (Berinert®)
D. Anything I can find in the pharmacy!

Key Takeaways

- **Key Takeaway #1**
  - If HAE diagnosis unknown, empiric treatment should consist of epinephrine, corticosteroids, and antihistamines
- **Key Takeaway #2**
  - Patients with significant laryngeal/oropharynx edema and airway issues, focus should be intubation/supportive care vs. pharmacological treatment
- **Key Takeaway #3**
  - No head to head studies have compared inpatient HAE treatments, selection based on formulary and drug availability

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ACE the Approach: Managing ACE-I-induced Angioedema

Jeremy P. Hampton, Pharm.D., BCPS
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UMKC School of Pharmacy / Truman Medical Center
Kansas City, MO

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CLINICAL CASE

- 59 year old AAF
- Inspiratory dyspnea, lingual edema, globus sensation with onset 1 hour prior to arrival
- Vital signs within normal range, maintaining 100% SpO_2 on 2L NC
- Home medications include lisinopril 20mg PO daily

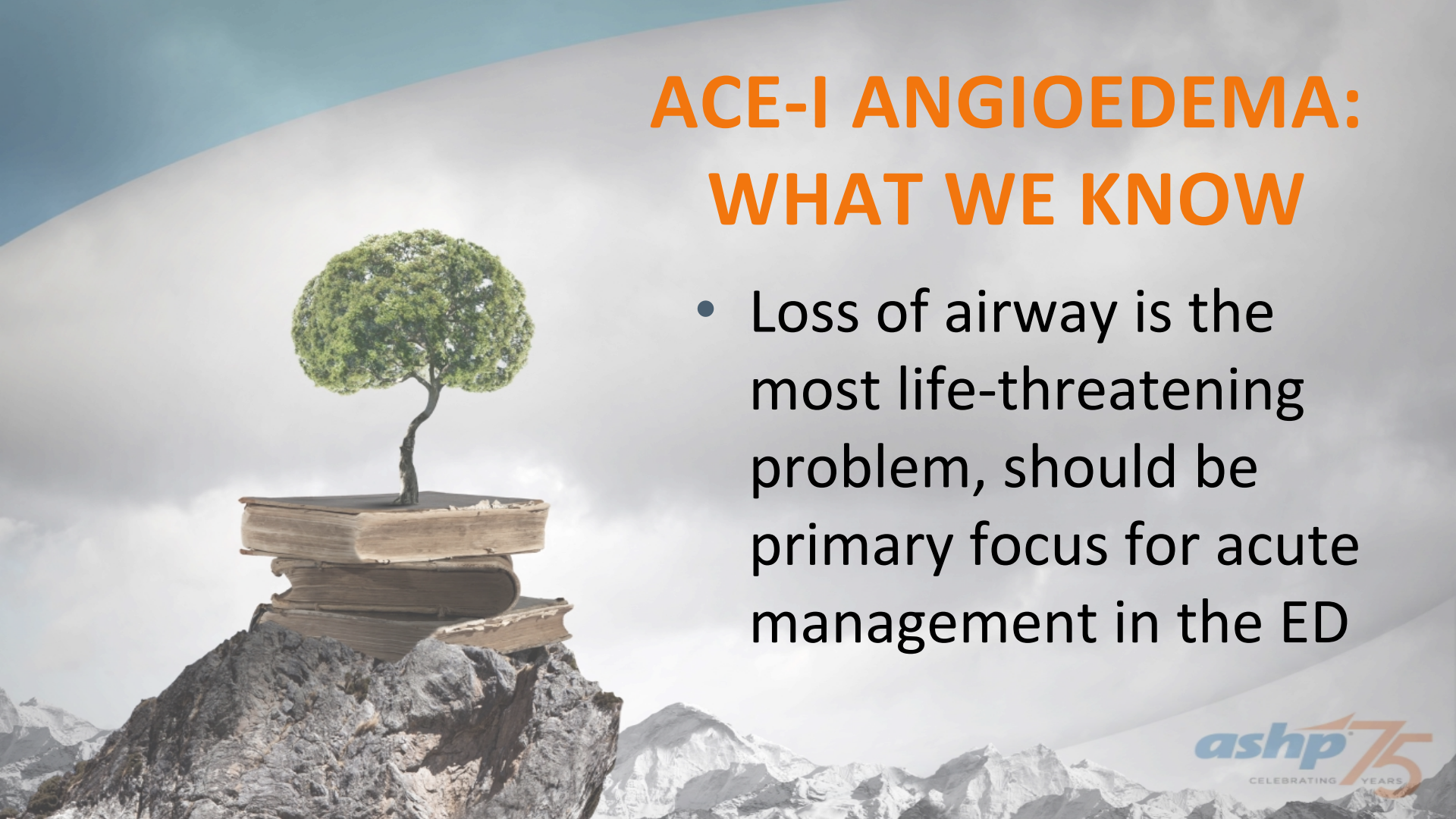
ACE-I ANGIOEDEMA: WHAT WE KNOW

- Likely precipitated by the accumulation of bradykinin
- Conventional treatment largely ineffective

ACE-I ANGIOEDEMA: WHAT WE KNOW

- Data limited, but possible treatments include FFP, kallikrein inhibitors, C1-esterase inhibitor concentrate, and icatibant

FFP – fresh frozen plasma



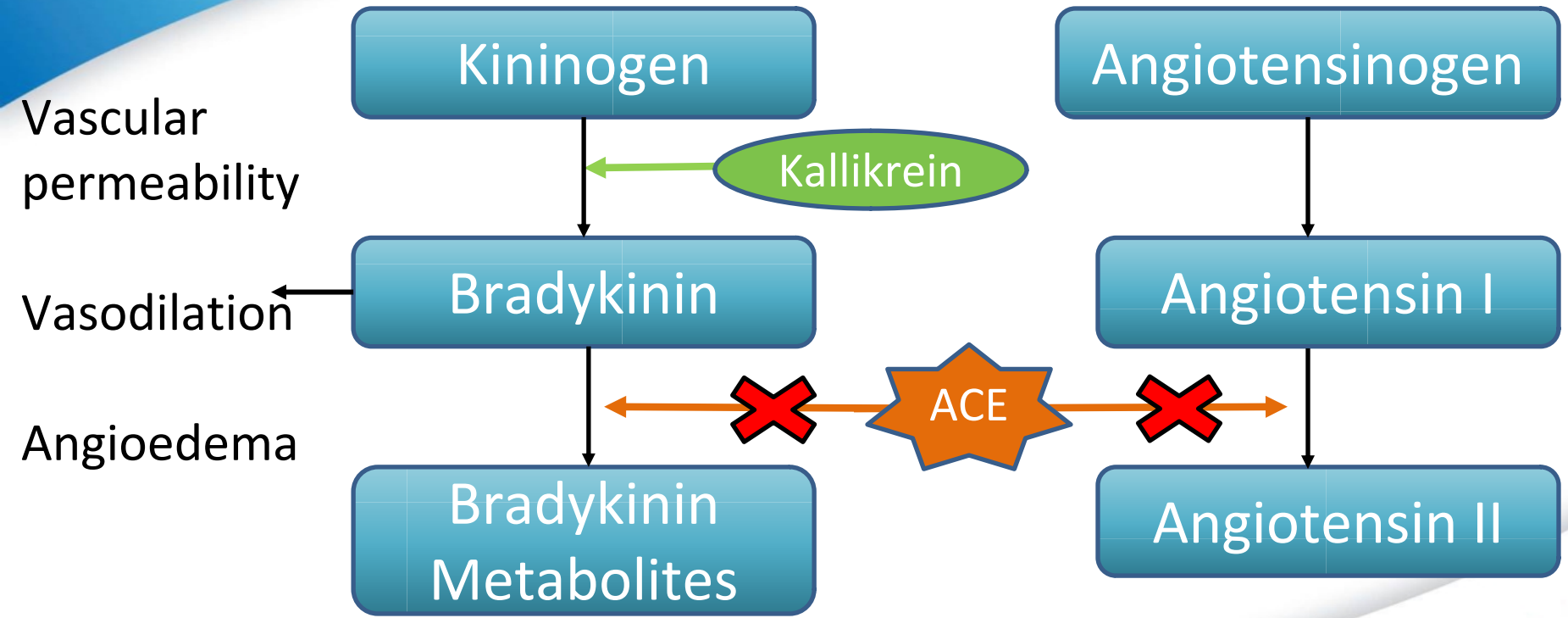
ACE-I ANGIOEDEMA: WHAT WE KNOW

- Loss of airway is the most life-threatening problem, should be primary focus for acute management in the ED

FLIGHT PLAN

- Mechanism and defining characteristics
- Possible treatment options and available data
- Where we are today and possible approach to care

ACE-I ANGIOEDEMA MECHANISM



HISTAMINE vs. BRADYKININ

- IgE mediated
- Pruritic urticaria common
- Responsive to ”standard” treatment
- Idiopathic, drug-induced (NSAIDS, aspirin), allergic

- Not associated with IgE
- Increased bradykinin production or insufficient degradation
- No urticaria
- Not responsive to ”standard” treatment

CHOOSE YOUR WEAPON

- FFP
- Ecallantide
- C1 Esterase Inhibitor Complex
- Icatibant

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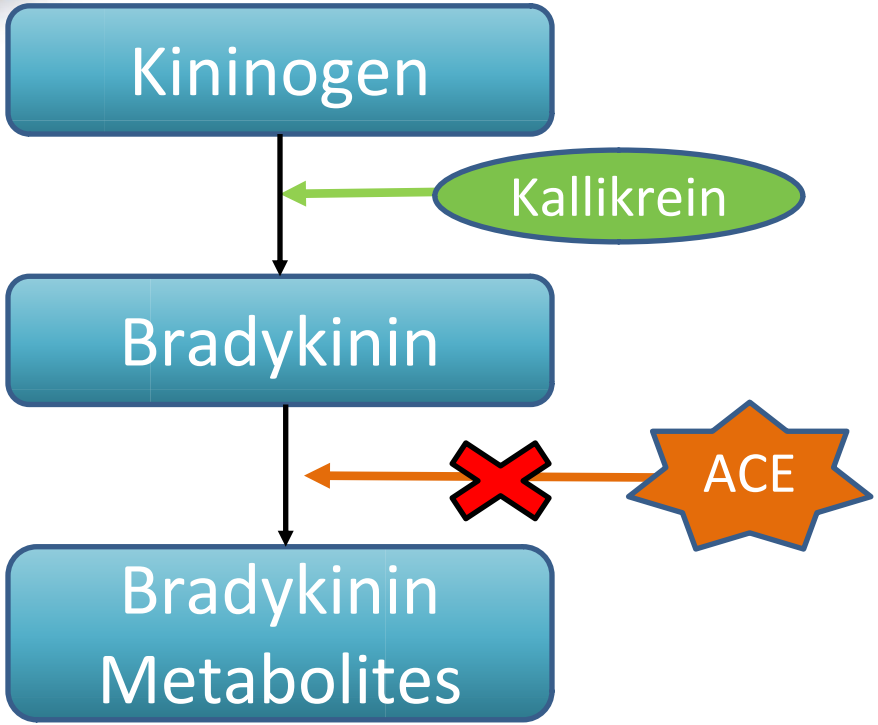
FRESH FROZEN PLASMA

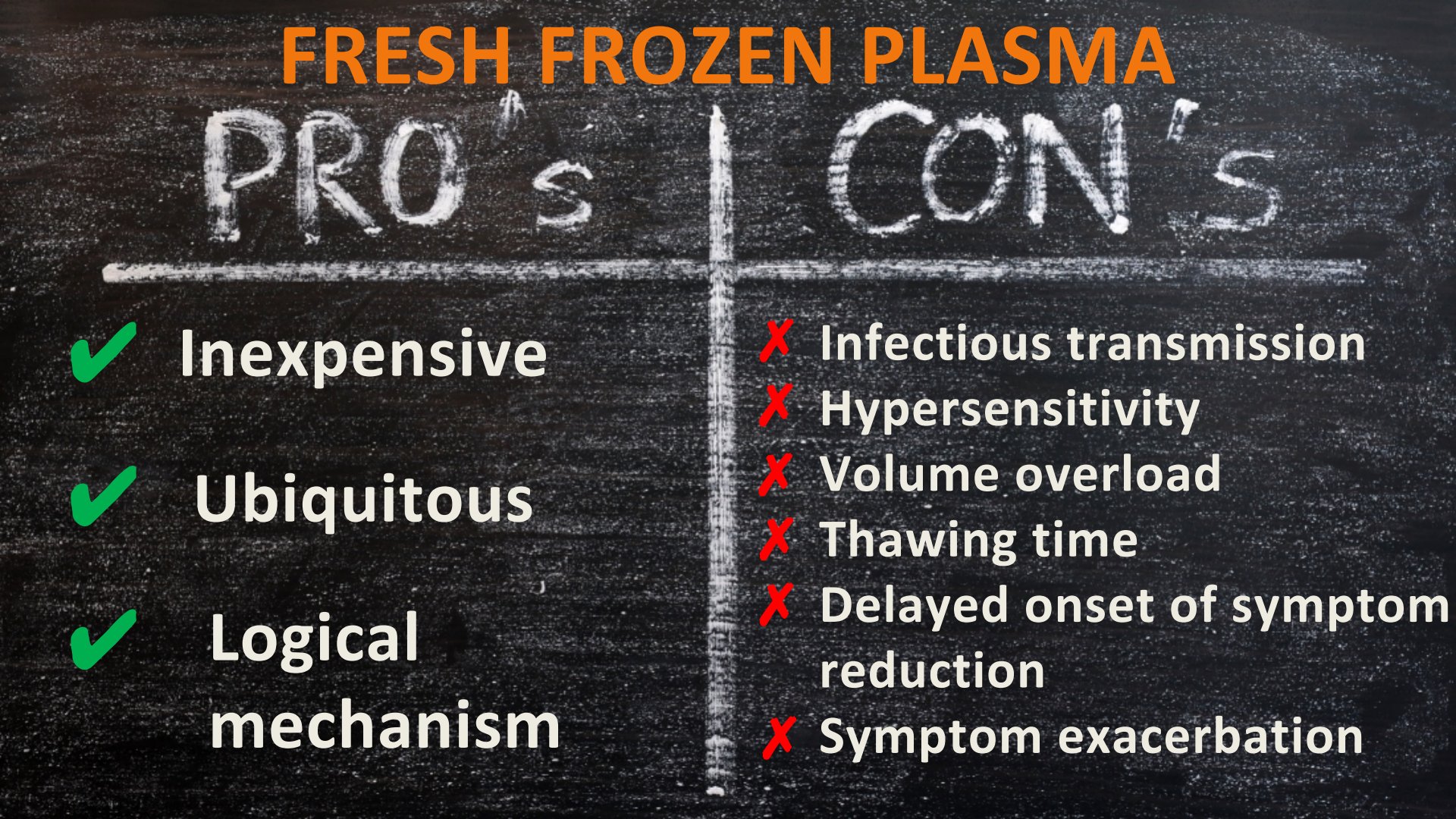


- Provides kininase II

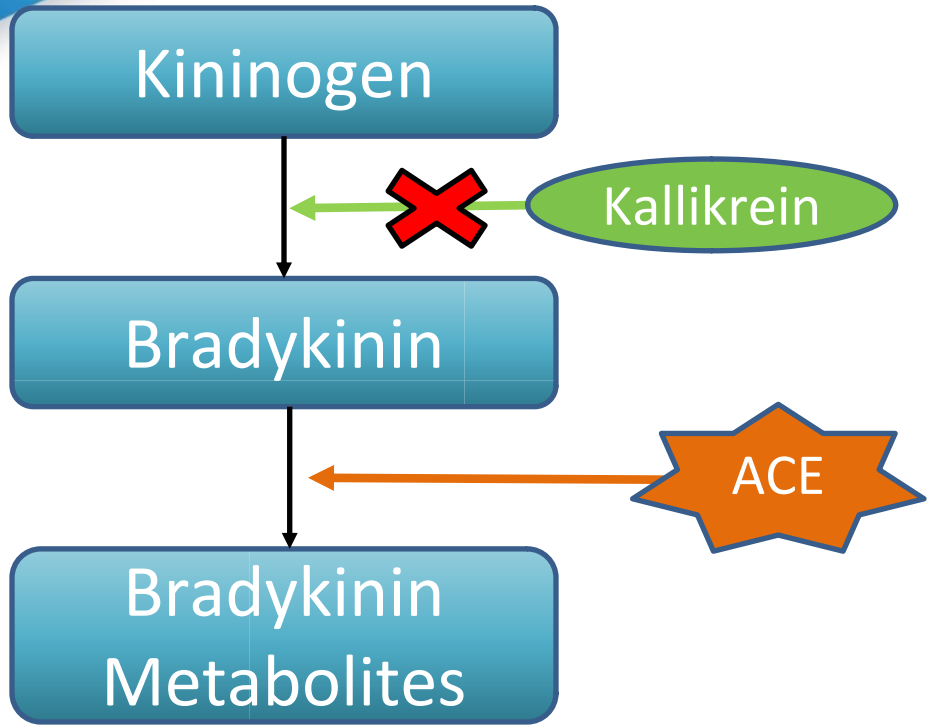
FRESH FROZEN PLASMA

- Limited evidence
  - 4 case reports, 10 patients[1]
  - Average dose 1-4 units (10-15 ml/kg)
  - Initial improvement – median 2 hours
  - Lack of good controls

FRESH FROZEN PLASMA



ECALLANTIDE



- Kallikrein inhibitor

ECALLANTIDE

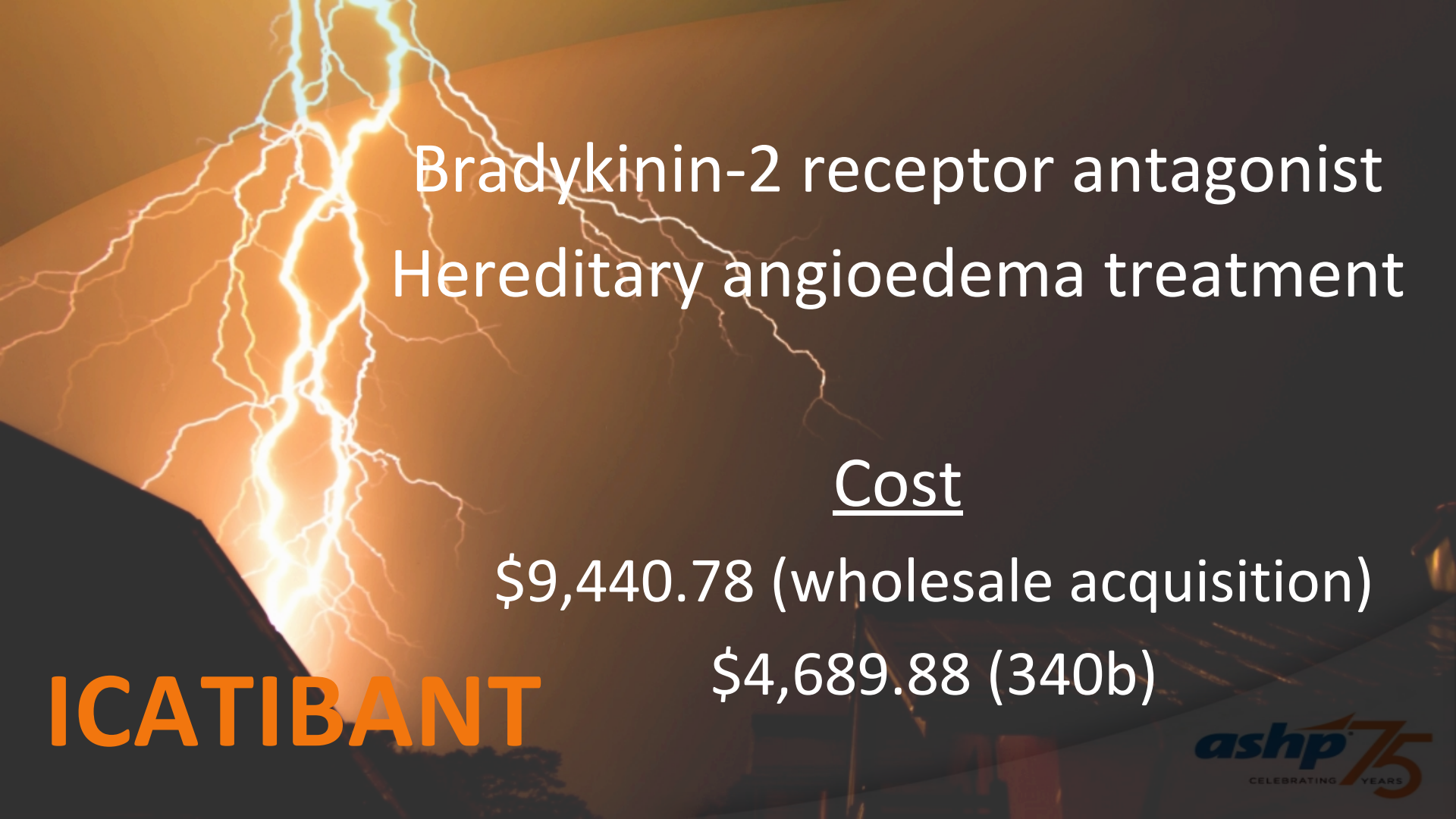
- Bernstein, et al[2]
  - Randomized, triple-blind, placebo-controlled
  - Ecallantide 30mg (n=26) vs placebo (n=24)
  - Primary end point – discharge within 4 hours
    - 8 (31%) ecallantide, 5 (21%) placebo – Not significant
  - Open label ecallantide if symptoms worsening
    - 11 (42%) ecallantide, 13 (54%) placebo

ECALLANTIDE

- Lewis et al.[3] - multicenter, phase 2, double-blind trial
- Ecallantide 10mg (n=20), 30mg (n=19), 60mg (n=19), vs placebo (n=18)
- Primary endpoint – discharge within 6 hours
- Study terminated: High response rates in all arms
- High rate of adverse effects
  - New or worsening angioedema – n=20 ecallantide; n=4 placebo

C1 ESTERASE INHIBITOR CONCENTRATE

- Blocks conversion of kininogen to bradykinin
- 2 case reports, 2 case series[1]
  - Total 23 patients
  - 22 patients - symptom improvement mean of 80 minutes
  - 1 patient – no symptom improvement, no further details
  - No adverse events reported
- Phase 3 recruiting, estimated completion late 2018



ICATIBANT

Bradykinin-2 receptor antagonist

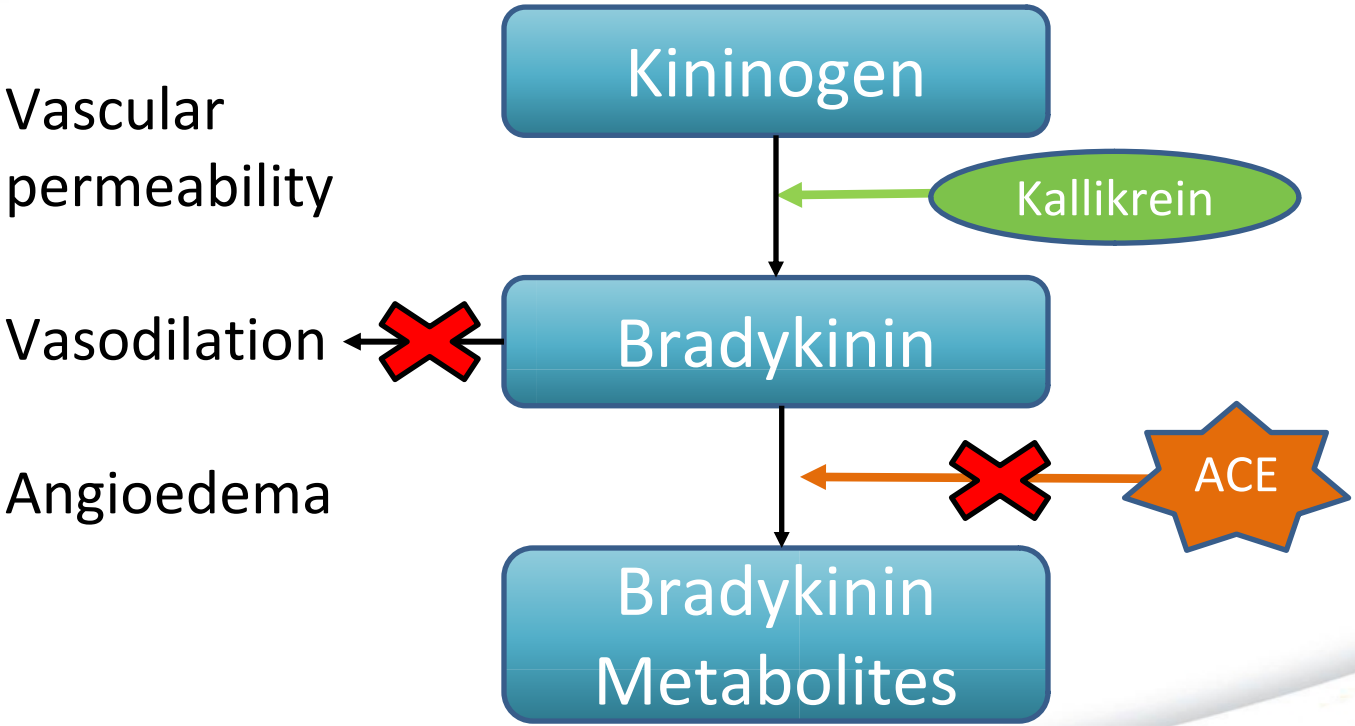
Hereditary angioedema treatment

Cost

$9,440.78 (wholesale acquisition)

$4,689.88 (340b)

ICATIBANT


Vascular permeability
Kininogen
Kallikrein
Vasodilation
Bradykinin
Angioedema
ACE
Bradykinin Metabolites

ICATIBANT EVIDENCE

- Case reports
- 3 case series
- 1 published, phase-II, randomized controlled trial
- 1 published, phase-III, randomized controlled trial

ICATIBANT – CASE REPORTS

- 26 patients[1]
  - 25 with symptom improvement, range 10-30 minutes
  - 1 without improvement

ICATIBANT – CASE SERIES

Bas et al[4]

- 47 patients (historical comparator)
  - Standard treatment
  - Full resolution – 33 hours
  - Airway intervention – 5 patients
- 8 patients, icatibant 30mg subcutaneously
  - Initial symptom relief – 50.6 +/- 21 minutes
  - Full resolution – 4.4 hours
  - Airway intervention – zero patients

ICATIBANT – CASE SERIES

DeBard et al.[5]

Pre-protocol

- 44 patients
- 18 admitted
- 6 (13.6%) airway intervention
- LOS – 7.7 days
- Cost - $17,878

Post-protocol

- 7 patients (icatibant)
- Zero airway intervention
- LOS – 0.5 days
- Cost - $5,951

ICATIBANT – CASE SERIES

Bova et al.[6]

Icatibant 30mg SQ following standard treatment

- 13 patients
- Symptom onset to icatibant – 3 hours
- Icatibant to onset of relief – 30 minutes
- Full resolution – 5 hours

Standard treatment (historical)

- 10 patients, 27 episodes
- Symptom onset to initial relief – 11 hours
- Full resolution – 54 hours

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ICATIBANT – PHASE 2 RCT

Bas et al.[7]

- Multicenter, double-blind, double-dummy
- Icatibant 30mg vs. “standard therapy”
- Primary end point
  - Time to complete resolution of symptoms

ICATIBANT – PHASE 2 RCT

Icatibant 30mg SQ

- 13 patients
- Primary end point – 8 hours*
- Complete resolution within 4 hours – 5 (38%)†
- Onset of relief – 2 hours§

Prednisolone 500mg + Clemastine 2mg

- 14 patients
- Primary end point – 27.1 hours
- Complete resolution within 4 hours – zero
- Onset of relief – 11.7 hours

*P = 0.002 † P = 0.02 § P= 0.03

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ICATIBANT PHASE 3 RCT

Sinert et al.[8]

- 31 centers, 4 countries
- Randomized 1:1 to icatibant 30mg or placebo, both administered subcutaneously

ICATIBANT PHASE 3 RCT

- Primary endpoint
  - Time to meet discharge criteria
- Secondary endpoint
  - Time to onset of symptom relief
  - Occurrence of airway intervention

ICATIBANT PHASE 3 RCT

Icatibant 30mg SQ

- 60 patients
- Primary end point – 4 hours†
- Onset of relief – 2 hours¥

Placebo

- 58 patients
- Primary end point – 4 hours†
- Onset of relief – 1.6 hours¥

† P =0.63 ¥ P=0.57

ICATIBANT PHASE 3 RCT

- Median time from attack onset to study drug
  - Placebo: 7.9h [range, 2.0 – 12.4]
  - Icatibant: 7.8h [range, 1.7 – 12.2]
- 1 patient (icatibant group) received airway intervention
  - 4.75 hours after attack onset
  - 1.5 hours after icatibant administration

ICATIBANT PHASE 3 RCT

- Author's conclusion:
  - Icatibant had no appreciable benefit in treating ACE-I-induced angioedema


NOW WHAT?

Limited evidence

Intubation avoidance

PREDICTING AIRWAY RISK – CASE SERIES

- Kieu, et. al.[9]
- Assess predictors for airway intervention
  - Time of presentation
  - High-risk clinical signs and symptoms
  - Anatomical regions in the head and neck that may indicate need for intubation

PREDICTING AIRWAY RISK – CASE SERIES

- 311 adult patients diagnosed with ACE-induced angioedema
- 52 patients (16.7%) required airway intervention
- Presenting within 4 hours of symptom onset correlated with 2-fold increase in likelihood of requiring intubation

PREDICTING AIRWAY RISK – CASE SERIES

- Highest risk symptoms
  - Dysphagia
  - Dysphonia
  - Globus sensation
  - Drooling
  - Respiratory distress

PREDICTING AIRWAY RISK – CASE SERIES

- Highest risk anatomical locations
  - Tongue
  - Soft palate
  - Vallecula
  - Aryepiglottic folds
  - True vocal cords
- Lowest risk locations
  - Face
  - Lower lip
  - Upper lip


WHERE DOES THIS LEAVE US?

RETURN TO THE CASE

- Lisinopril discontinued
- Icatibant 30mg SQ administered
- Subjective report of symptom reduction within 45 minutes
- Admitted, monitored in ICU, discharged following day

WHAT WOULD YOU DO?

Key Takeaway #1

- ACE-inhibitor-induced angioedema is mediated by bradykinin accumulation and is largely unresponsive to “conventional” therapy

Key Takeaway #2

- There is a paucity of data regarding the use of FFP, ecallantide, C1 esterase inhibitor concentrate, and icatibant in ACE-I-induced angioedema

Key Takeaway #3

- Consideration *may* be given for use of icatibant in patients who are at high risk of requiring airway intervention, e.g., patients presenting within 4 hours of symptom onset, who present with drooling, respiratory distress, dysphagia, dysphonia, or globus sensation, or who present with affected tongue, soft palate, vallecula, aryepiglottic folds, or true vocal cords.

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THOUGHTS?
QUESTIONS?