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Speaker Introduction

Katie Dwyer, PharmD

PGY-2 Emergency Medicine Resident

Katie completed her pharmacy schooling at The University of Kansas, School of Pharmacy. Where she obtained at BS in pharmaceutical studies and her PharmD. Following pharmacy school, she completed her post-graduate year one training at University of Chicago Medicine. Currently she is completing her second year of post graduate training at University of Utah Health, where she is specializing in emergency medicine.

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UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Katie Dwyer
November 16, 2021

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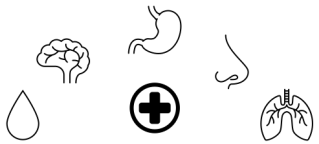
TXA in the [trauma] Bay



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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Katie Dwyer:**
    - None
  - **CE mentor, Cole Sloan:**
    - None
- Off-Label Uses of Medications
  - Tranexamic acid

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Learning Objectives

- **Pharmacist Objectives:**
  - Discuss the pharmacokinetic and pharmacodynamic considerations of tranexamic acid
  - Analyze the use of tranexamic acid based on the literature available
  - Construct a recommendation for the use of tranexamic acid based on a patient case
- **Technician Objectives:**
  - Recognize the formulation and administration technique of tranexamic acid
  - Outline the various indications for use of tranexamic acid in the emergency department
  - Evaluate how to prioritize safe and efficient delivery of medications for patients receiving tranexamic acid

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Background of Tranexamic Acid (TXA)

Use dates back 50 years

Hereditary bleeding disorders
Heavy menstrual bleeding

Inexpensive

Reduced blood loss

Thromb Res 2015; 135(2):231-242.
Haematologica 2020 105(5):1201-1205.

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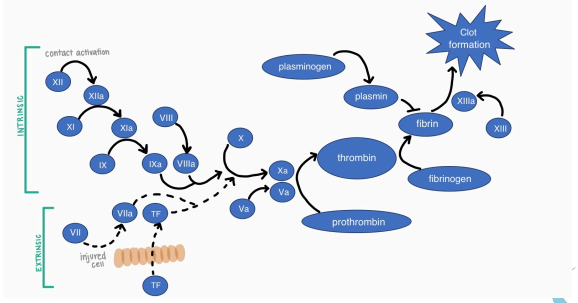
Antifibrinolytics



Heart Lung Vessel. 2014;6(1):5-7.
Image: Created by the presenter

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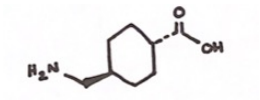
Tranexamic Acid

- Synthetic lysine amino acid derivative
- Mechanism of Action:
  - Competitively inhibits the activation of plasminogen to plasmin by binding at the lysine bindings sites on plasminogen
  - Displaces plasminogen from the surface fibrin
  - Inhibits the dissolution of the fibrin matrix



TXA package insert. Exela Pharma Sciences. 2019.
Micromedex TXA entry. 2021
Image: Created by the presenter

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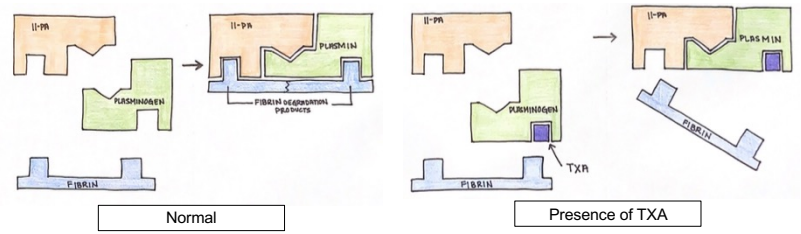
Tranexamic Acid



Normal | Presence of TXA

tt-PA: tissue plasminogen activator
TXA: tranexamic acid

Image: Created by presenter

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Tranexamic Acid

- Onset of action:
  - PO 2.5 hours
  - IV 5 minutes
- Duration of fibrinolysis:
  - PO 24 hours
  - IV 17 hours
- Dosing:
  - Indication dependent
- Contraindications:
  - Subarachnoid hemorrhage
  - Active intravascular clotting
  - Hypersensitivity reactions
- Adverse Effects:
  - Nausea, vomiting, diarrhea, allergic dermatitis, giddiness, hypotension, thromboembolic events, seizures, anaphylaxis,

PO: oral
IV: intravenous

TXA package insert. Exela Pharma Sciences. 2019.
Micromedex TXA entry. 2021

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Tranexamic Acid

FDA® Approved Indications:

- Hemophilia for short term use during or following tooth extraction
- Menorrhagia

Off-Label Indications:

- Hemorrhage, angioedema, hemoptysis, epistaxis, intracranial hemorrhage, perioperative blood loss

TXA package insert. Exela Pharma Sciences. 2019.
Micromedex TXA entry. 2021

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Audience Response Question

Tranexamic acid exerts its action on the clotting cascade through:

a. Binds to thrombin, potentiating the conversion of fibrinogen to fibrin
b. Forms a complex with plasminogen preventing the inhibition of fibrin
c. Irreversibly binds to fibrin, blocking its effects
d. Forms a complex with plasminogen, potentiating the effects of fibrin

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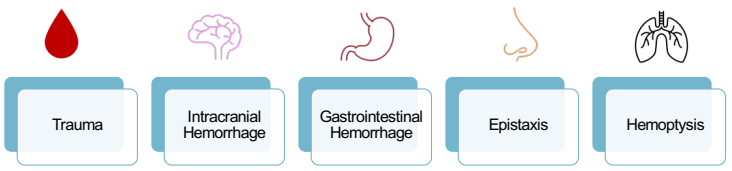

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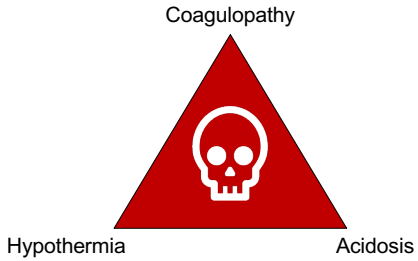
Lethal Triad aka Trauma Triad of Death



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Chin J Traumatol. 20 (2017) 125-132.

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Trauma Induced Coagulopathy

- Principal cause for preventable death following trauma
- Driven by tissue injury and hypoperfusion
- Modulated by the protein C pathway
- Hyperfibrinolysis associated with massive transfusion and poor outcomes

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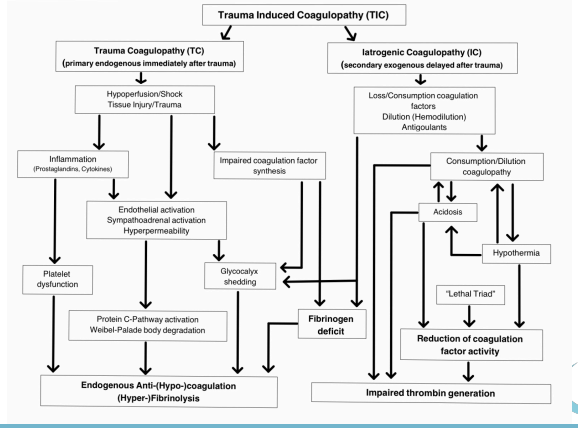

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Hemorrhagic Shock

	Class I	Class II	Class III	Class IV
Blood loss (mL)	Up to 750	750-1500	1500-2000	> 2000
Blood loss (% blood volume)	Up to 15	15-30	30-40	> 40
Heart rate (beats/minute)	< 100	100-120	120-140	>140
Blood pressure (mmHg)	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (breaths/min)	14-20	20-30	30-40	> 35
Urine output (mL/hour)	>30	20-30	30-40	>35
Mental Status	Slightly anxious	Mildly anxious	Anxious/Confused	Confused/Lethargic

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Massive Transfusion Protocol

- Patients with Class III or IV
- Hypotension following 1-2 L of crystalloid fluids
- Definition:
  - 10 units of blood in 24 hours
  - 5 units of blood in 4 hours

Blood Products:

- Packed red blood cells (PRBC)
- Fresh frozen plasma (FFP)
- Cryoprecipitate
- Platelets
- Factor Products

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PROPPR Trial

Objective

- A 1:1:1 ratio of plasma:platelets:red blood cells is non-inferior to a 1:1:2 ratio in trauma patients receiving massive transfusion

Design

- Pragmatic, phase 3, multicenter, randomized control trial. At 12 level 1 trauma centers in the United States.

Population

- N = 630, highest level of trauma

Intervention

- 1:1:1 arm (n = 338), 1:1:2 arm (n = 342)

JAMA 2015;313:471-482

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PROPPR Trial

Conclusion

- Early administration of plasma, platelets, RBCs did not result in a significant difference in mortality at 24 hours (12.7% vs 17.0%) or at 30 days (10.2% vs. 26.1%)
- More patients achieved hemostasis in the 1:1:1 group (86.1% vs 78.1%; p=0.06)

Limitations

- Providers were unblinded following randomization
- Underpowered to determine < 10% mortality benefit at 24 hours and 30 days

Take away

- A transfusion ratio of 1:1:1 can be used in trauma patients

JAMA 2015;313:471-482

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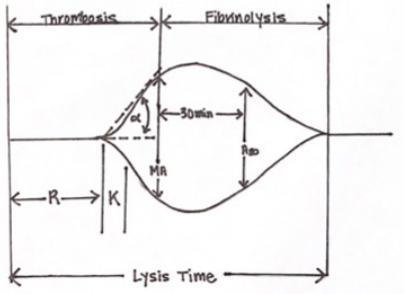
Thromboesltography (TEG)
Rotational Thromboesltography (ROTEM)



Thromboelastography in Trauma. Surgical Critical Care Evidence-Based Guidelines Committee.
AJH. 89(2)2014:228-232.
Image: Created by the presenter

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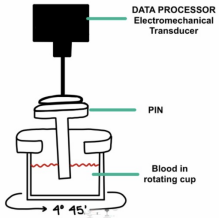
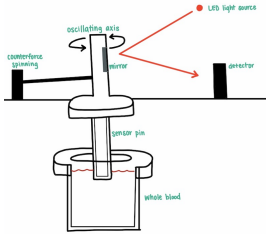
TEG



ROTEM



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Thromboesltography (TEG)
Rotational Thromboesltography (ROTEM)

Suggested TEG-guided Transfusion

TEG Value	Transfuse
TEG-ACT > 140	FFP
R time > 10	FFP
K time > 3	Cryoprecipitate
Alpha-angle < 53	Cryoprecipitate +/- platelets
MA < 50	Platelets
LY30 > 3%	Tranexamic acid

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Guidelines

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Guideline Recommendations

European

- Initial management of patients with massive hemorrhage is FFP and PRBCs in a ratio of at least 1:2 as needed
- TXA should be administered to patients who are bleeding or at risk within 3 hours of initial injury
  - 1 g over 10 minutes followed by 1 g over 8 hour

EAST

- High ratio of plasma and platelets to PRBCs to reduce mortality
- Conditionally recommend TXA as a hemostatic adjunct

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Major Studies

- CRASH-2
- MATTERs

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CRASH-2

Objective

- Assess the effects of the early administration of TXA on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients

Design

- Multicenter, randomized, placebo-controlled trial
- Conducted within 274 hospitals and 40 countries

Population

- N = 20,211, adult trauma patients with or at risk of significant hemorrhage

Intervention

- Placebo 0.9% sodium chloride vs TXA 1 g followed by 1 g over 8 hours

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Lancet. 2010;376:23-32

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CRASH-2

Conclusion

- Significant reduction in all cause mortality and deaths from bleeding
- TXA was associated with significant reduction in the odds of any cause of death (14.5% vs 16%; p=0.0035)

Limitations

- Deaths due to bleeding and vascular occlusive events could have been misclassified
- Bleeding onset is difficult to deduce in trauma patients, leading to error
- Portion of patients did not receive PRBCs
- Conducted outside of the U.S.

Take Away

- TXA improves survival when administered in less than 3 hours after injury in patients with significant hemorrhage

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Lancet. 2010;376:23-32

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MATTERs

Objective

- Report the experience of the use of TXA in the combat setting and to characterize its effect on measures for coagulopathy and survival

Design

- Retrospective observational study conducted in Afghanistan

Population

- N = 896, received 1 U PRBCs

Intervention

- TXA 1g bolus, repeated as indicated per the treating physician

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Arch Surg. 2012; 147:113-119

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MATTERs

Conclusion

- Decreased 48-hour mortality in patients treated with TXA. Overall (11.3% vs. 18.9%; p=0.004), massive transfusion subgroup (10.4% vs. 23.5%; p=0.003)
- PE (2.7% vs 0.3%; p=0.03); DVT (2.4% vs 0.2%; p=0.001)
- TXA in conjunction with blood products improves measures of coagulopathy and survival

Limitation

- European guidelines were released during the study period
- Retrospective design of the study

Take Away

- Early administration of TXA following severe vascular disruption with hemorrhage should be implemented into practice

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PE: pulmonary embolism
DVT: deep vein thrombosis

Arch Surg. 2012; 147:113-119

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Audience Response Question

36-year-old male presents via AirMed from scene following a high-speed ATV rollover. The patient was not helmeted and found pinned under the ATV. In flight the patient's mental status continued to decline and he is becoming increasingly tachycardic. BP 101/70 HR 112 RR 12 GCS 7. The accident occurred around 1300 and they arrive in the trauma bay at 1830. The trauma team asks about the utility of TXA, which recommendation would you provide?

a. The patient is too far out from their injury to receive any benefit from TXA
b. Administer TXA 1 gram over 10 minutes followed by 1 gram over 8 hours
c. TXA is associated with more harm than benefit in trauma patients
d. TXA is not indicated for any trauma patients

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Intracranial Hemorrhage

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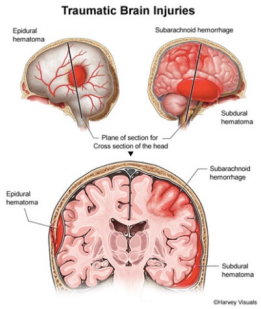
Pathophysiology



Emerg Med Clin North Am. 2012;30(3):771-794.
Image: https://www.flickr.com/photos/143428029@N08/32245205335/in/photolist

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Guidelines

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Guidelines

AHA Management of Spontaneous ICH	Management of Severe Traumatic Brain Injury	Reversal of Antithrombotic in Intracranial Hemorrhage
• Urgent treatment of time-sensitive issues including, reversal of coagulopathy should be initiated in the emergency department • No mention of TXA	• Hyperosmolar therapy • Hypotension should be avoided • No mention of TXA	• Thrombolytic activators – Cryoprecipitate or antifibrinolytics • TXA 10-15 mg/kg IV over 20 minutes

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Stroke. 2015;46:2032-2060.
Neurosurgery. 2017;80(1):6-15.
Critical Care Medicine: December. 2016;44(12):2251-2257.

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Major Studies

- CRASH-2
- CRASH-3
- TICH-2

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CRASH-2

Objective
- Quantify the effect of an early short course of TXA on intracranial hemorrhage in patients with TBI

Design
- Nested within the CRASH-2 trial

Population
- N = 270; patients meeting inclusion criteria in CRASH-2 *with* a TBI

Intervention
- TXA 1g over 10 minutes followed by 1g over 8 hours or matching 0.9% normal saline

Conclusion
- Overall saw lower hemorrhage growth in the TXA group
- Cerebral ischemia could not be ruled out, but TXA was not associated with harm

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BMJ. 2011;343:d3795

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CRASH-3

Objective
- Effects of TXA on head injury related death, disability and adverse effects in patient with TBI

Design
- Multicenter, double-blinded, parallel-group, randomized controlled trial

Population
- N = 12,737; TBI randomized within 3 hours of injury

Intervention
- TXA 1 g over 10 minutes followed by 1 g over hours vs matching placebo

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Lancet 2019; 394: 1713-23

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CRASH-3

Conclusion

- Head injury related death in patients within 3 hours of injury (18.5% vs 19.8%; CI 0.80-1.0)
- Mild-moderate GCS 9-15 (p=0.03) and bilateral pupil reactivity (p=0.03)
- All vascular occlusive events (1.6% vs 1.6%; CI 0.74-1.28)

Limitation

- Patients were sicker or had more severe injruies

Take Away

- TXA did not improve mortality but did not cause increased harm to trauma patients with traumatic brain injury

GCS: Glasgow coma scale

Lancet 2019; 394: 1713-23

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TICH-2

Objective

- To see if intravenous TXA reduces death and dependence when given within 8 hours of spontaneous ICH

Design

- International, randomized, double-blinded, placebo-controlled, parallel group trial

Population

- N = 2,325; adults with acute ICH

Intervention

- 1 g IV bolus followed by 1g over 8 hours or matching placebo

ICH: intracranial hemorrhage

Lancet. 2018;391(10135):2107-2115.

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TICH-2

Conclusion

- Functional status at day 90 was no different between groups
- Hematoma expansion at day 2 (25% vs 29%; p = 0.0300)
- Mean hematoma volume expansion from baseline to 24 hours (3.72 mL vs 4.90 mL; p=0.0432)
- Mortality at 7 days (9% vs 11%; p=0.0406)

Limitation

- Heterogenous patient populations with severe strokes

Take Away

- TXA improved early mortality, reduced hematoma expansion, and was associated with fewer adverse events

Lancet. 2018;391(10135):2107-2115.

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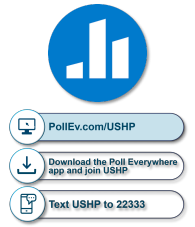
Audience Response Question

Results of the CRASH-3 trial demonstrated:

a. Higher rates of pulmonary embolism, and deep vein thrombosis in the TXA treatment group
b. Greatest survival benefit seen in those treated with TXA 3 hours or more following injury
c. Mortality benefit when TXA was given within the first 3 hours following injury
d. No difference in dependency at hospital discharge between groups



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Gastrointestinal Hemorrhage

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Pathophysiology

Categorized based on anatomic and pathophysiologic factors

Upper GIB

- Originates: esophagus, stomach, duodenum
- Causes: NSAIDs, variceal hemorrhage, Mallory-Weiss tear, neoplasms

Lower GIB

- Originates: small bowel, colon, rectum
- Causes: diverticular disease, angiodysplasia or angiectasia, neoplasms, colitis, anorectal lesions, fissures, rectal ulcers

NSAID: non-steroidal anti-inflammatory drug

World J Gastroenterol. 2012 Mar 21;18(11): 1154–1158.

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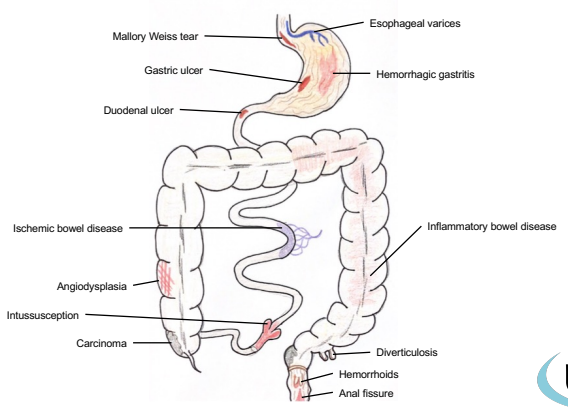

Image: Created by the presenter

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Guidelines

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American College of Gastroenterology

Acute Lower Gastrointestinal Bleeding	Variceal Hemorrhage	Bleeding Ulcer
• Hemodynamic resuscitation • PRBCs transfused to maintain Hgb > 7	• Blood volume resuscitation should be promptly undertaken, goal Hgb > 8 • In patients with significant coagulopathy and/or thrombocytopenia plasma and platelets can be transfused	• Blood transfusion to target Hgb > 7

Hgb: hemoglobin

Am J Gastroenterol. 2016 April ; 111(4): 459–474.
Am J Gastroenterol. 2007;102:2096–2102.
Am J Gastroenterol. 2012;107:345–360.

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Major Studies

HALT-IT

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HALT-IT

Objective
- Does IV TXA reduce 5-day death due to bleeding in adult patients with acute gastrointestinal hemorrhage?

Design
- International, multicenter, randomized, placebo-controlled trial

Population
- N = 12,009; significant lower and/or upper GIB

Intervention
- TXA 1g in 100 mL over 10 minutes, then 3g TXA in 1 L at 125 mg/hr over 24 hours
- Matching placebo

Lancet 2020; 395: 1927–36.

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HALT-IT

Conclusion
- 5-day mortality due to bleeding (4% vs 4%; RR = 0.99)
- Arterial thromboembolic events (0.7% vs 0.8%; RR = 0.92)
- Venous thromboembolic events (0.8% vs 0.4%; RR 1.85, NNH = 250)

Limitation
- Sample size originally calculated based on all cause mortality
- Majority of patients enrolled had variceal bleeding due to liver disease

Take Away
- There is no benefit of giving TXA on 5-day mortality in patients with acute GIB

Lancet 2020; 395: 1927–36.

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Audience Response Question

For which of the following cases should TXA be avoided?

a. 58-year-old M with known NASH cirrhosis presenting with gastrointestinal hemorrhage
b. 47-year-old M trauma patient in class IV hemorrhagic shock
c. 61-year-old F trauma patient with a subarachnoid hemorrhage
d. 22-year-old M with multiple gunshot wounds to the head, neck and abdomen

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Epistaxis

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Pathophysiology

- Caused by ruptured vessels within the nasal mucosa
- Ruptures can be spontaneous, trauma, medication(s), or secondary to other comorbidities or malignancies
- Two types: anterior and posterior

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StatPearls [Internet]. Last updated Aug 2021.

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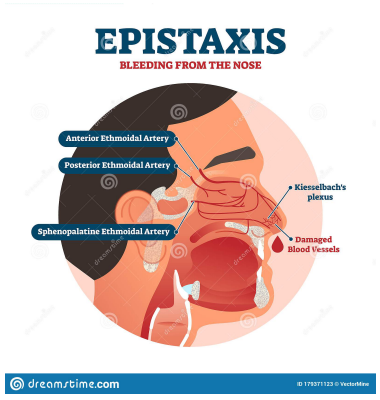

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Image: flickr.com

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Guidelines

- First line treatment includes combination of direct nasal compression, application of topical agents, cautery or electrocautery, or packing
- TXA used topically to control nosebleeds
- Topical application of TXA provided more effective for patients on antiplatelet medications (i.e., aspirin, clopidogrel)

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Major Studies

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NoPAC

Objective
- Effectiveness of topical intranasal TXA in reducing the need for anterior nasal packing in adult patients

Design
- Randomized, double-blind, parallel group, placebo-controlled trial

Population
- N = 496; spontaneous atraumatic epistaxis

Intervention
- TXA for topical (intranasal) use prepared as a clear colorless solution at 100 mg/mL

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NoPAC

Conclusion
- Packing in the ED (43.7% vs 41.3%)
- Hospital admission (43.3% vs 45.5%)
- Recurrent epistaxis (19.5% vs 16.1%)

Limitations
- Underpowered to detect a difference

Take Away
- Topical TXA is no more effective than placebo at controlling bleeding and reducing need for anterior nasal packing

ED: Emergency department

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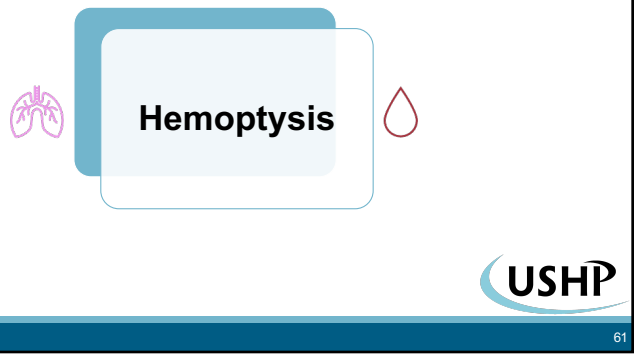

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Pathophysiology

- Bleeding originates in either the pulmonary circulation or the bronchial circulation
- Causes:
  - Pulmonary infection, bronchitis, bronchiectasis, tuberculosis, bronchogenic carcinoma, pulmonary edema, and pulmonary embolism

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Hemoptysis. *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill; 2018.
Hemoptysis. *Principles and Practice of Hospital Medicine*. 2nd ed. New York, NY: McGraw-Hill; 2017.

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Management

- Dependent on the severity and origin of bleeding
- Immediate goals protect the patient's airway
- Later locate and control the site of bleeding
- Bleeding should resolve with treatment of the underlying cause
- Nebulized TXA can be used

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Hemoptysis. *Harrison's Principles of Internal Medicine*. 20th ed. New York, NY: McGraw-Hill; 2018.
Hemoptysis. *Principles and Practice of Hospital Medicine*. 2nd ed. New York, NY: McGraw-Hill; 2017.

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Wand et al. (2018)

Objective
- Assess the effectiveness of TXA inhalations for hemoptysis treatment

Design
- Randomized, double-blind, placebo-controlled trial

Population
- N = 47, hemoptysis of varying etiology

Intervention
- Nebulized TXA 500 mg/5 mL given 3 times daily
- Nebulized normal saline 5 mL given 3 times daily

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Chest. 2018;154(6):1379-1384.

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Wand et al. (2018)

Conclusion

- Resolution within 5 days of admission (96% vs 50%; p<0.0005)
- Hospital length of stay (5.7 days vs 7.8 days; p=0.046)

Limitations

- Patients with massive hemoptysis (> 200 mL/24 hr), hemodynamic instability, or respiratory instability were excluded

Take Away

- Nebulized TXA has been effective for controlling hemoptysis, but more data is needed for its effect in massive hemoptysis

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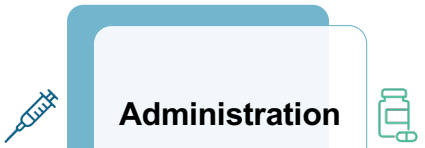

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Storage

How it's supplied:

- Vial 1000 mg/10 mL
- Tablet 650 mg
- Oral suspension 25 mg/mL
  - 500 mg tablet mixed with 20 mL of water
- Oral solution (5%) 50 mg/mL
  - Diluting 5 mL of (10%) 100 mg/mL TXA with 5 mL sterile water

Locations:

- Trauma Bay – vials only
- Central Pharmacy

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Preparation

Trauma, ICH, GIB	Epistaxis	Hemoptysis
		

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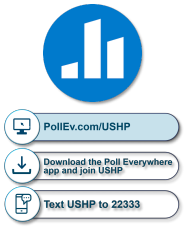
Audience Response Question

True or False – The load for TXA must be compounded in the IV center for administration.

a. True
b. False



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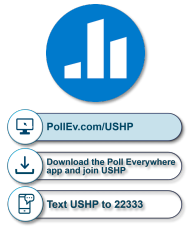
Audience Response Question

A nurse sends a med message to the technician requesting a dose of TXA STAT for a patient with a nosebleed in the ED. Which of the following options represents the most safe and efficient delivery of this medication?

a. Fill the med order, obtain pharmacist verification and tube a vial to the ED STAT
b. Send a vial on the next run for delivery – the last one just left so it'll be at least 60 minutes
c. Inform the nurse the medication is in the trauma bay automated dispensing cabinet
d. Option A and C depending on the institution



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Conclusion

- TXA was shown to improve mortality in trauma patients presenting with hemorrhagic shock if administered within 3 hours of injury
- TXA is safe for use in patients with intracranial hemorrhage
- There is no mortality benefit and an increased risk of thromboembolic events in patients who receive TXA for gastrointestinal hemorrhage
- TXA dose not improve outcomes in patients with epistaxis
- There is insufficient data to conclude any benefit in the administration of TXA for massive hemoptysis

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Thank You!

Thank you to Cole Sloan, my mentor on this presentation.

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TXA in the [trauma] Bay

CE Code: (USHP will fill in)

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