UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

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November 5, 2019

Getting High on Mountain Rescue: Pharmacologic considerations in emergency medicine and transitions of care

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Disclosure

Relevant Financial Conflicts of Interest

- CE Presenter, Lauren McClure, PharmD:
  - None
- CE mentor, Colgan Sloan, PharmD, BCPS:
  - None

Off-Label Uses of Medications

- Acetazolamide, dexamethasone, ketamine, tranexamic acid, gentamicin, cefazolin, ceftriaxone

Learning Objectives: Pharmacists

- Recognize acute mountain sickness and potential sequelae
- Examine the utility of tranexamic acid in a patient case
- Design a prophylactic antibiotic regimen for open fractures given a patient case

Learning Objectives: Technicians

- Describe the transitions of care involved in remote rescue operations
- Explain the risk factors for developing Acute Mountain Sickness
- Distinguish appropriate ketamine vial concentrations based on patient care area

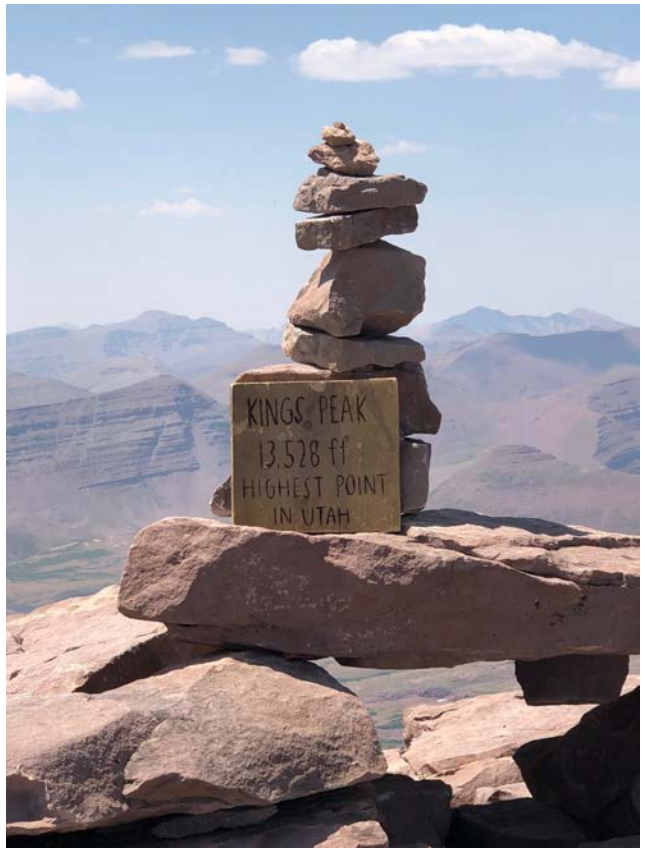
Patient Case

Jack and Diane are hiking Kings Peak over Labor Day Weekend on vacation from Austin, Texas. They arrive in Salt Lake City on Saturday morning and drive out to the Uintas to camp at the trailhead before making their ascent.

Wilderness Medicine

Patient Case

- Jack starts feeling light-headed, decreased appetite, with increasing weakness
- As they reach the peak, symptoms progress:
  - Occasional vomiting
  - Moderate headache
  - Mild weakness/fatigue
  - Dizziness



What is going on? What is the first thing he should do?

- A) Relax, take a break– this is no big deal
- B) Recognize moderate acute mountain sickness and move to lower elevation immediately
- C) Recognize mild acute mountain sickness - take acetazolamide and keep going
- D) Take a magnesium supplement

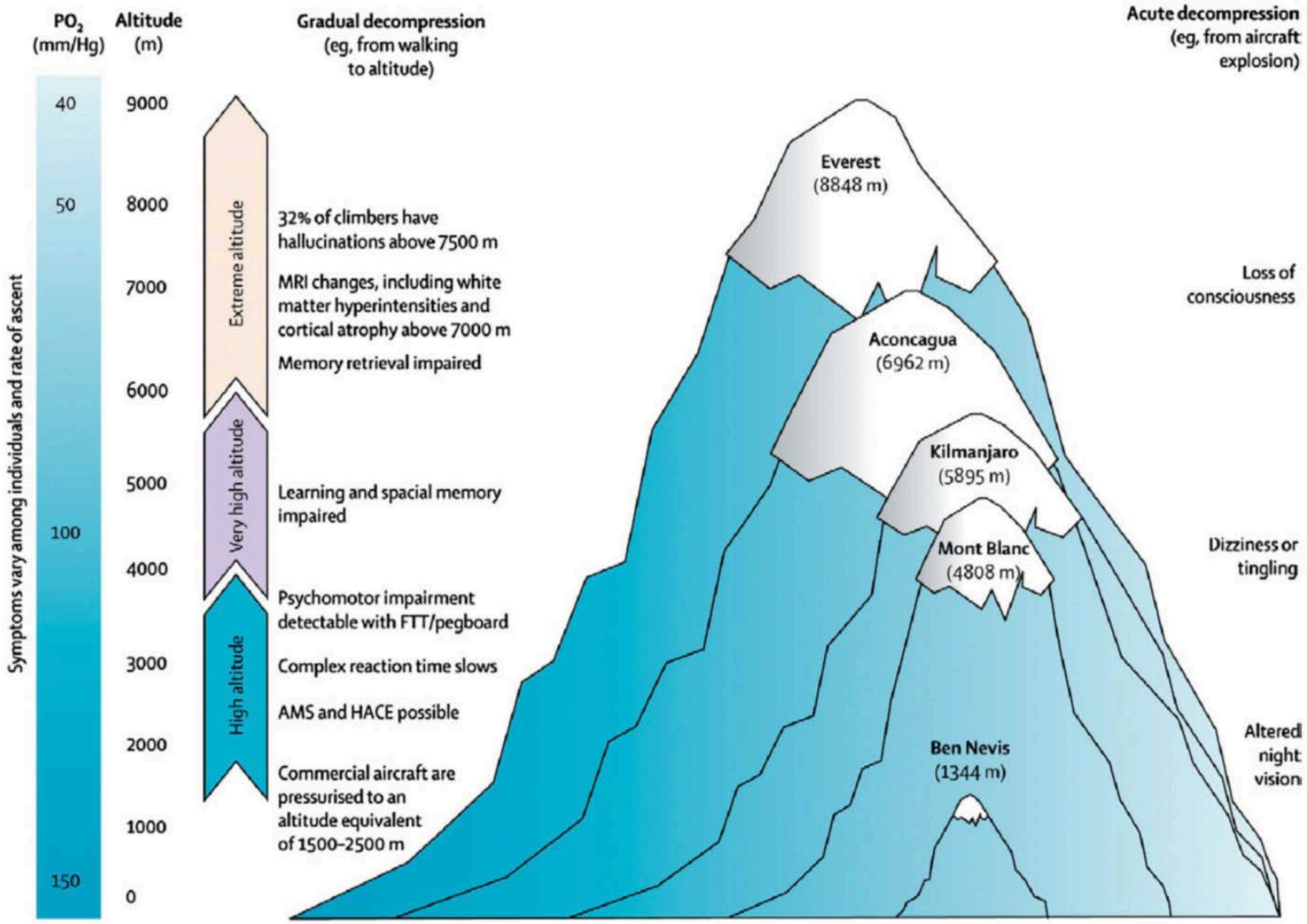
Acute Mountain Sickness (AMS)

- >2,500 m (8,200 feet)
- Within 5 days
- Potentially deadly consequences
  - High-altitude pulmonary edema (HAPE)
  - High-altitude cerebral edema (HACE)

Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84

Pathophysiology of AMS

Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84


PO2 (mm/Hg)
Altitude (m)
Gradual decompression (eg, from walking to altitude)
Acute decompression (eg, from aircraft explosion)
Symptoms vary among individuals and rate of ascent
40
50
100
150
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Extreme altitude
Very high altitude
High altitude
32% of climbers have hallucinations above 7500 m
MRI changes, including white matter hyperintensities and cortical atrophy above 7000 m
Memory retrieval impaired
Learning and spacial memory impaired
Psychomotor impairment detectable with FTT/pegboard
Complex reaction time slows
AMS and HACE possible
Commercial aircraft are pressurised to an altitude equivalent of 1500–2500 m
Everest (8848 m)
Aconcagua (6962 m)
Kilmanjaro (5895 m)
Mont Blanc (4808 m)
Ben Nevis (1344 m)
Loss of consciousness
Dizziness or tingling
Altered night vision

Risk Factors

- Speed of ascent
- Elevation reached
- Altitude naïve
- Prior AMS

*Sea-level fitness is NOT protective

Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84

2018 Lake Louise AMS Score

Symptom	Severity	Points
Headache	None	0
	Mild	1
	Moderate	2
	Severe, incapacitating	3
Gastrointestinal symptoms	Good appetite	0
	Poor appetite/nausea	1
	Moderate nausea/vomiting	2
	Severe n/v, incapacitating	3
Fatigue/weakness	None	0
	Mild	1
	Moderate	2
	Severe, incapacitating	3
Dizziness/light-headedness	None	0
	Mild	1
	Moderate	2
	Severe, incapacitating	3

High Alt Med Biol. 2018 Mar;19(1):4-6

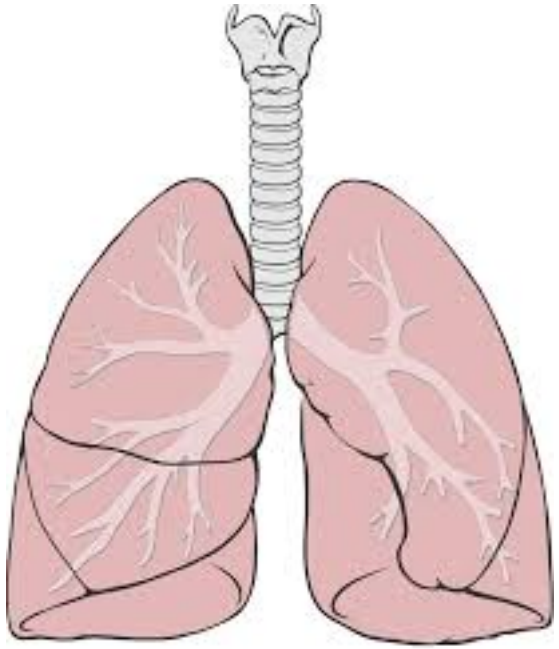
Identification

- AMS
  - Mild = 3-5
  - Moderate = 6-9
  - Severe = 10-12
- Progress to life threatening complications

Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84

High Altitude Pulmonary Edema (HAPE)

- AMS + pulmonary signs
  - Cough
  - Chest tightness
  - Congestion
- Incidence 0.01-5%



Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84

High Altitude Cerebral Edema (HACE)

- AMS + mental status change
  - Ataxia
  - Drowsiness
  - Stupor
- Incidence 0.5-1%
- Potentially fatal

Prog Cardiovasc Dis. 2010 May-Jun;52(6):467-84

AMS Prevention

Recommended

- Gradual ascent
- **Acetazolamide**
- Dexamethasone

Not recommended

- Inhaled budesonide
- Ginkgo biloba
- Acetaminophen

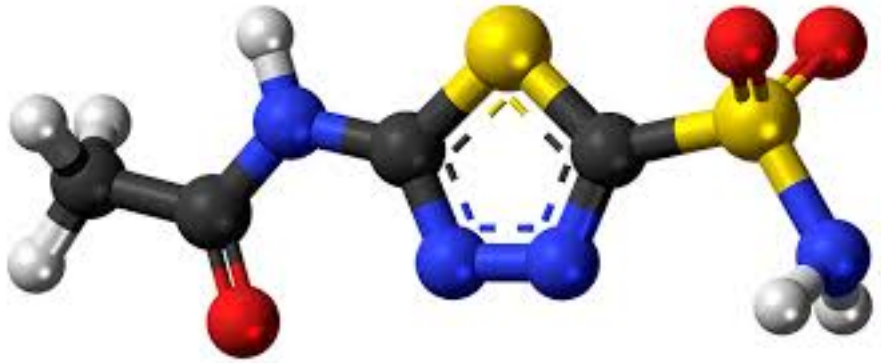
2019 Wilderness Medicine Society Practice Guidelines

Wilderness Environ Med. 2019 Jun 24. pii: S1080-6032(19)30090-0.

Acetazolamide

Facilitates acclimatization

Carbonic anhydrase inhibitor → Increases bicarbonate secretion → Induces metabolic acidosis → Stimulates ventilation



BMJ 2012;345:e6779
Ann Intern Med. 1992;116(6):461-465

Acetazolamide for AMS Prevention

- 2012: BMJ Meta Analysis
  - 11 randomized, placebo controlled trials
  - Acetazolamide 750mg, 500mg, 250mg daily
  - Lowest effective dose: 125mg BID
    - 4 trials
    - OR 0.36 (95% CI 0.28 – 0.46)
    - NNT = 6

BMJ 2012;345:e6779

Acetazolamide for AMS Prevention

- 2019: RADICAL Trial
  - Prospective, double blind, randomized, non-inferiority trial
  - 73 Trekkers to Everest Base Camp
  - Compared acetazolamide 62.5mg BID vs standard 125mg BID
  - Reduced-dose is non-inferior

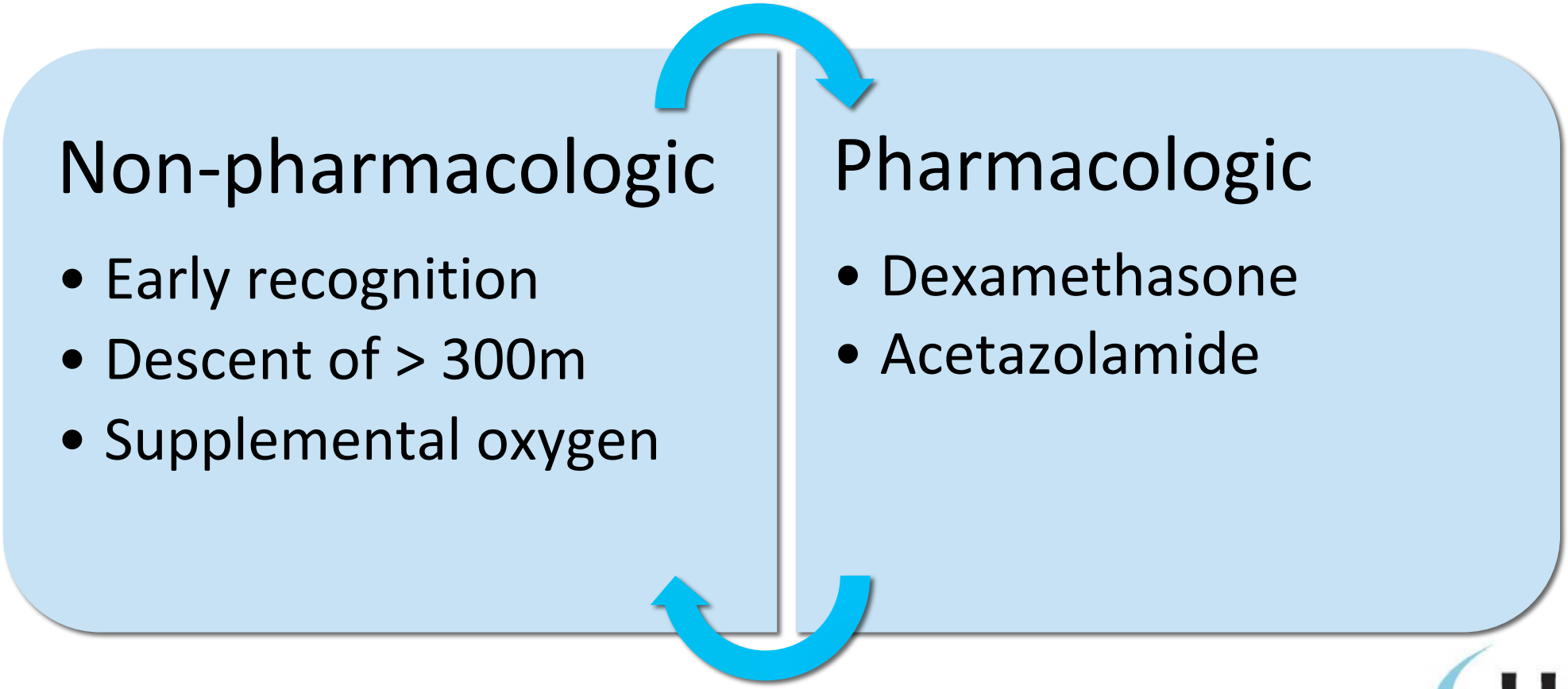
Wilderness Environ Med. 2019 Mar;30(1):12-21

Dexamethasone for AMS Prevention

- Exact mechanism of action in AMS is uncertain
- Does not facilitate acclimatization
- Recommended dose: 4 mg q12h
- Limited data
  - Ellsworth, et al 1987 – effective prevention (25% vs 77% incidence) of AMS at 4,392m

West J Med. 1991 Mar; 154(3): 289–293.
N Engl J Med 1989; 321:1707-1713
Am J Med. 1987 Dec;83(6):1024-30

Treatment



Wilderness Environ Med. 2019 Jun 24. pii: S1080-6032(19)30090-0.

Dexamethasone

- Standard of care
- Dose: 8mg IV, IM, or PO x1 then 4mg q6h
- Ferrazzini, 1987
  - 35 patients in Alps Valais at 4560m
  - Randomized, double blind, placebo controlled
  - 77% symptom reduction

West J Med. 1991 Mar; 154(3): 289–293
Br Med J (Clin Res Ed). 1987 May 30;294(6584):1380-2
N Engl J Med 1989; 321:1707-1713

Acetazolamide for AMS Treatment

- 2018 Meta-Analysis:
  - 2 randomized control trials
  - 25 total patients
  - Acetazolamide 250 mg BID
  - No clear effect on symptom reduction
    - Standard mean difference -1.15 (95% CI -2.56 – 0.27)

Cochrane Database Syst Rev. 2018 Jun 30;6:CD009567

28 YO M climbing at ~4000 m, with new onset dizziness, weakness, moderate headache, vomiting

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What risk factors did Jack have for developing Acute Mountain Sickness?

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Moving along…

- Diane decides they should move to a lower elevation
- Take the shortcut between Anderson Pass and Gunsight Pass
- Jack slips on the loose rocks and falls
- Diane can see bone sticking out of his leg → calls for help

Pre-hospital Emergency Transport
Chemical Restraints

Patient Case

- While attempting to establish IV access, Jack starts shouting and thrashing around, trying to exit the helicopter
- Flight crew is struggling to hold him down

- How do you want to handle this?

28 YO M, altered mental status, combative, with open fracture but no known past medical history

How do you choose to chemically restrain the patient?

A) Administer Fentanyl 100 mcg through an IO line

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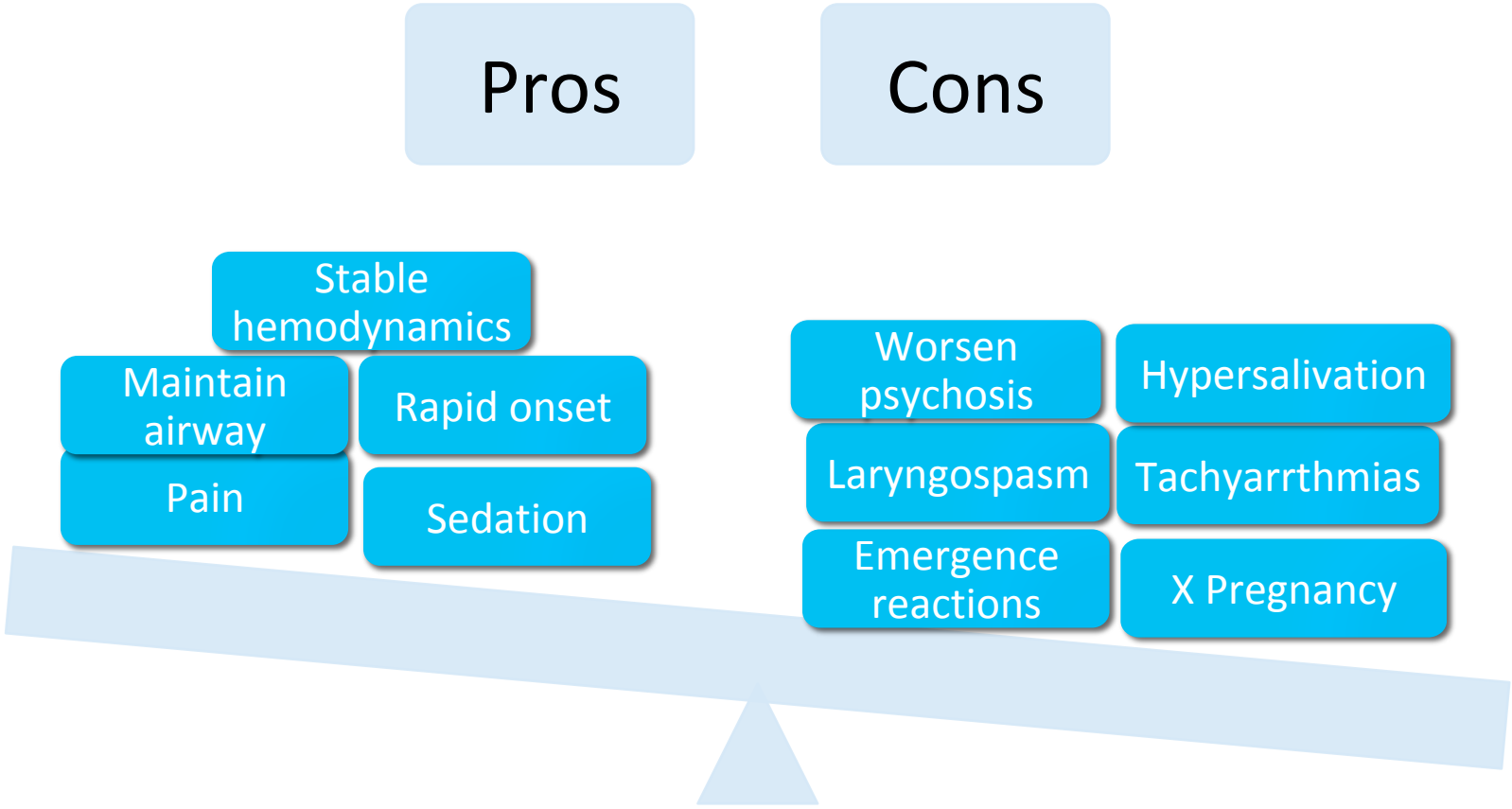
Ketamine

- Dissociative anesthetic
- Unique sedative and analgesic properties
- Noncompetitive antagonist at NMDA receptors

Front Hum Neurosci 2016;10:612

Ketamine for Agitation – Balancing Act



Front Hum Neurosci. 2016; 10: 612.

Ketamine – Dosing Basics in Agitation

	Intravenous	Intramuscular
Usual Dose	1-2 mg/kg	2-4 mg/kg
Onset	< 1 min	< 5 min
Duration	5-10 min	20-30 min

Ketamine for Agitation

- Typical dose ranges from 2-4 mg/kg IM
- Pre-hospital studies report intubation rates of 39-63%
  - Rates increase with increasing doses
- No increase in sedation above dissociation threshold
  - Not well established in IM administration
  - 1-1.5 mg/kg IV
  - Bioavailability: 93%

Clin Toxicol (Phila). 2019 Jul 23:1-5.

Why not reduce the dose?

- Case Series by O'Brien et al. 2019
  - Efficacy and safety of ketamine 2 mg/kg IM in the Emergency Dept
  - Successful sedation of the agitated patient
  - Results:
    - 13/15 (87%) had adequate sedation without needing intubation
    - Median total dose of 157.5 mg, 2 mg/kg
    - 11/15 (73%) received IM ketamine as a second-line agent

Clin Toxicol (Phila). 2019 Jul 23:1-5.

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You decide to administer Ketamine 4mg/kg (320 mg) IM

- 10 mg/mL → 32 mL
- 100 mg/mL → 3.2 mL

Pre-hospital Emergency Transport
Uncontrolled Bleeding

Patient Case

- Patient has calmed down − but is increasingly hypotensive and the team is concerned for internal bleeding

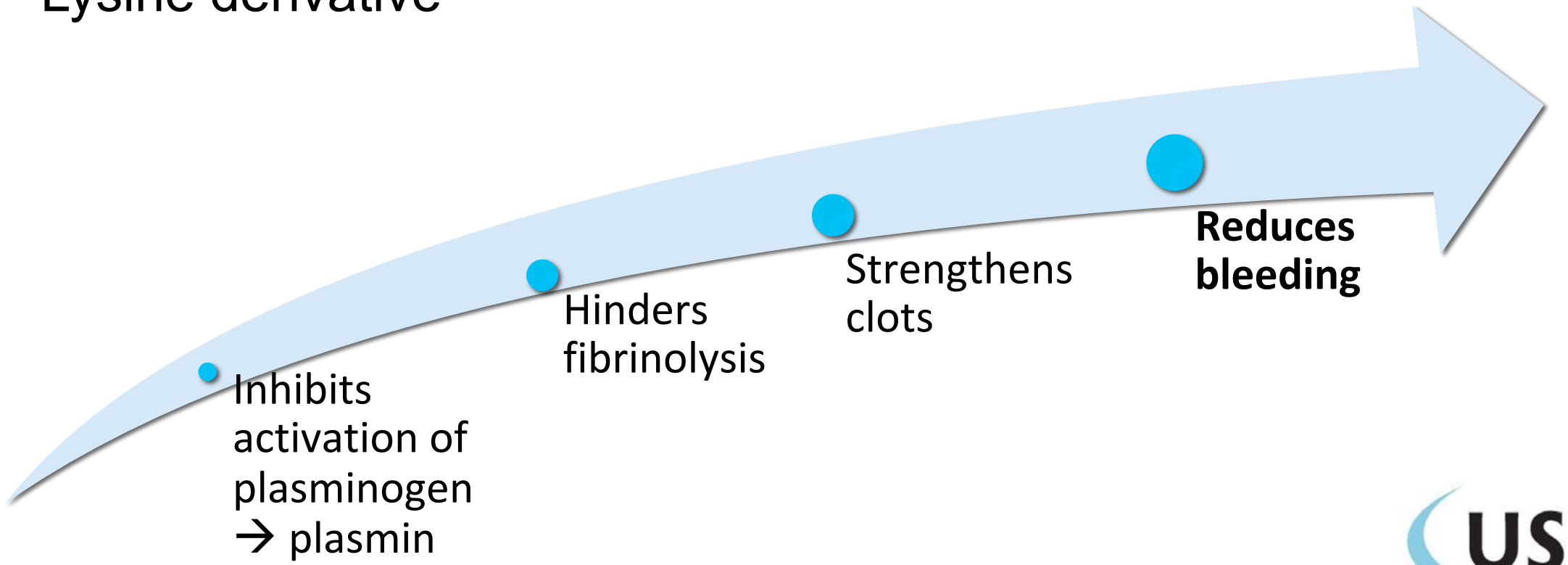
Remote Damage Control Resuscitation

- Recombinant Factor VII → no survival benefit in trauma setting
- Plasma → COMBAT trial terminated early for futility
- Antifibrinolytic agents
  - Aprotinin → withdrawn from market in 2007
  - ε-aminocaproeic acid → did not reduce transfusions in initial studies
  - **Tranexamic acid** (TXA) → perioperative studies reduced need for blood transfusion

https://clinicaltrials.gov/ct2/show/NCT01838863
J Trauma Acute Care Surg. 2015 Jun;78(6 Suppl 1):S70-5

Tranexamic Acid (TXA)

Lysine derivative



J Trauma Acute Care Surg. 2015 Jun;78(6 Suppl 1):S70-5

CRASH-2

Double blind, randomized, placebo controlled trial

Evaluated TXA in 20,211 trauma patients

Intervention:

- TXA 1g IV over 10 min + 1g IV over 8 hours
- Placebo

Outcomes

- Primary: death in hospital within 4 weeks of injury
- Described bleeding, vascular occlusion, multiorgan failure, head injury

The Lancet. 2010. 376(9734):23-32.

CRASH-2

- Death in hospital within 4 weeks:
  - TXA: 14.5%
  - Placebo: 16.0%
  - RR 0.91, 95% CI 0.85-0.97, P=0.0035

Secondary Outcome	TXA	Placebo	P value
Vascular occlusive events (MI, CVA, PE, DVT)	1.7%	2.0%	0.084
Surgical interventions	47.9%	48.0%	0.79
Blood transfusion	50.4%	51.3%	0.21

Lancet. 2010. 376(9734):23-32.

CRASH-2

Early administration of TXA reduces risk of death from bleeding

- < 1 hour from injury
  - RR 0.68 (0.54-0.86
- 1-3 hours from injury
  - RR 0.79 (0.60-1.04)
- > 3 hours from injury
  - RR 1.44 (1.04-1.99)
- Composite − within 8 hours
  - RR 0.85 (0.76-0.96)

Lancet. 2010. 376(9734):23-32.

Traumatic Brain Injury (TBI)

- Initial concern for futility in TBI patients, potential risk of increased thrombotic stroke
- Systematic review and meta-analysis (March 2019)
  - Pooled 5 RCTs for 917 total patients
  - TXA reduced rate of hematoma expansion
    - RR 0.77, CI 0.61-0.98, p=0.03
  - No difference in pooled clinical outcomes of surgery, mortality, neurologic outcome
  - No difference in thrombotic event rate

World Neurosurg. 2019 Mar;123:128-135

Ongoing TXA Trials

Trial	Purpose	Outcome
CRASH-3	TXA within 8 hours of TBI	Mortality Disability
PATCH-Trauma	Pre-hospital TXA	Mortality Functional recovery
STAAMP	Pre-hospital TXA	Mortality Clinical outcomes

28 YO M, s/p traumatic injury, now with BP 86/60, concern for bleeding, has received 2L of normal saline

What do you recommend for this patient?

A) Start norepinephrine gtt at 0.5 mcg/kg/min

B) Give TXA 1g IV bolus

C) Administer 1 unit of plasma

D)Give another 1L bolus of NS

Patient Case

Pt condition is tenuous, but not worsening. Paramedic team calls report to the University of Utah Emergency Department's charge nurse, and prepares for hospital arrival

Trauma Activation

Pictures included in this section may be graphic to some viewers

Patient Case

Neuro: GCS 14 (E4, V5, M5)

Cardiac: BP 89/65, HR 110

Respiratory: Airway intact, SpO2: 94%

MSK: Type 3 open fracture of R femur, multiple lacerations

FAST exam: Negative

Chest XR: mild pulmonary edema

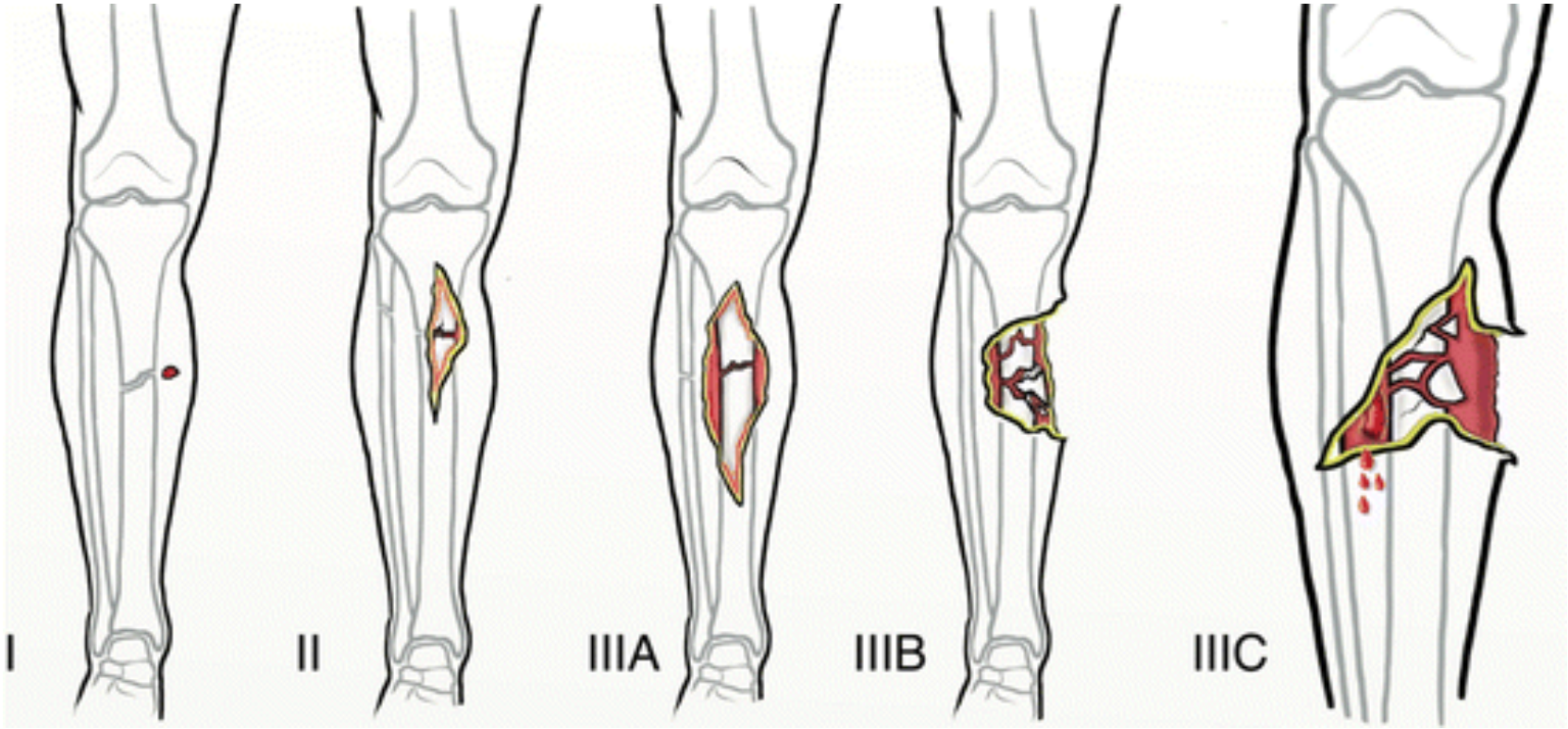
What medications do you want to administer before patient goes to the OR?

Open Fractures

Bone fragments exposed to the outside environment

https://coreem.net/core/open-fractures/

Gustilo-Anderson Classification



Kanakaris NK, Giannoudis PV. “Open Fractures.” Trauma and Orthopaedic Classifications: A Comprehensive Overview. 2014; 487-493

Eastern Association for the Surgery of Trauma (EAST) Guidelines

Gustilo-Anderson Type	Recommended antibiotic
Type 1 and 2	First generation cephalosporin
Type 3	First generation cephalosporin + Once daily aminoglycoside
Potential Clostridial contamination = add penicillin	

Hoff WS, et al. J Trauma 2011;70(3):751-754

Concerns with Aminoglycosides

- Hypermetabolic trauma patients
  - Barletta et al: subtherapeutic in 21%
  - Toschlong et al: subtherapeutic in 58.2%

- Nephrotoxicity and acute kidney injury (AKI)
  - 5-15% incidence with aminoglycoside use
  - High risk of dosing errors
  - Trauma patients at increased risk of AKI

J Trauma. 2000;49:869-872
J Trauma. 2003;55:255-262
Curr Opin Crit Care. 2017;23(6):447-456

Velmahos et al.

- Design: prospective nonrandomized study
- Population: Patients admitted to a surgical ICU
- Groups: >1 antibiotic for > 24 h vs. 1 antibiotic for 24 h
- Results: prolonged prophylaxis with multiple agents is an independent risk factor for development of resistant infections
  - (OR 2.13, 95% CI 1.22-3.74, p=0.008
- No difference in sepsis, organ failure, death

Arch Surg. 2002;137:537-542.

Velmahos et al.

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- Population: Patients admitted
- Groups: >1 antibioti for 24 h
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  - 3.74, p=0.008
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More is NOT Better

Arch Surg. 2002;137:537-542.

Rodriguez et al.

- Single center retrospective cohort study
- Implemented a new open fracture protocol
  - Type 1 or 2: Cefazolin
  - Type 3: Ceftriaxone
  - Removed aminoglycosides, vancomycin, and penicillin
- Outcomes
  - Aminoglycoside and glycopeptide use
  - Rate of surgical site infections (SSI)

Rodriguez, et al. J Trauma Acute Care Surg. 2013;77(3):400-408

Rodriguez et al.

	Pre-Protocol (per fracture event)	Post-Protocol (per fracture event)	P value
Aminoglycoside / glycopeptide use	**53.5% (54/101)**	**16.4% (12/73)**	**0.0001**
SSI Rate	**20.8% (21/101)**	**24.7% (18/73)**	**0.58**
By Gustillo Class			
Type 1	29.4% (5/17)	6.7% (1/15)	0.09
Type 2	8% (2/25)	20% (4/20)	0.24
Type 3	29.7% (11/37)	40% (8/20)	0.62
Not graded	13.6 (3/22)	27.8% (5/18)	0.09

Rodriguez, et al. J Trauma Acute Care Surg. 2013;77(3):400-408

Rodriguez et al.

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	13.6 (3/22)	27.8% (5/18)	0.09

Ceftriaxone is Enough

Rodriguez, et al. J Trauma Acute Care Surg. 2013;77(3):400-408

28 YO M, 80 kg, NKDA, Type 3 open fracture of R femur

What prophylactic antibiotic regimen would be <u>LEAST</u> appropriate for this patient?

- A) Cefazolin 2g IV
- B) Cefazolin 2g IV + Gentamicin 320 mg
- C) Ceftriaxone 2g IV
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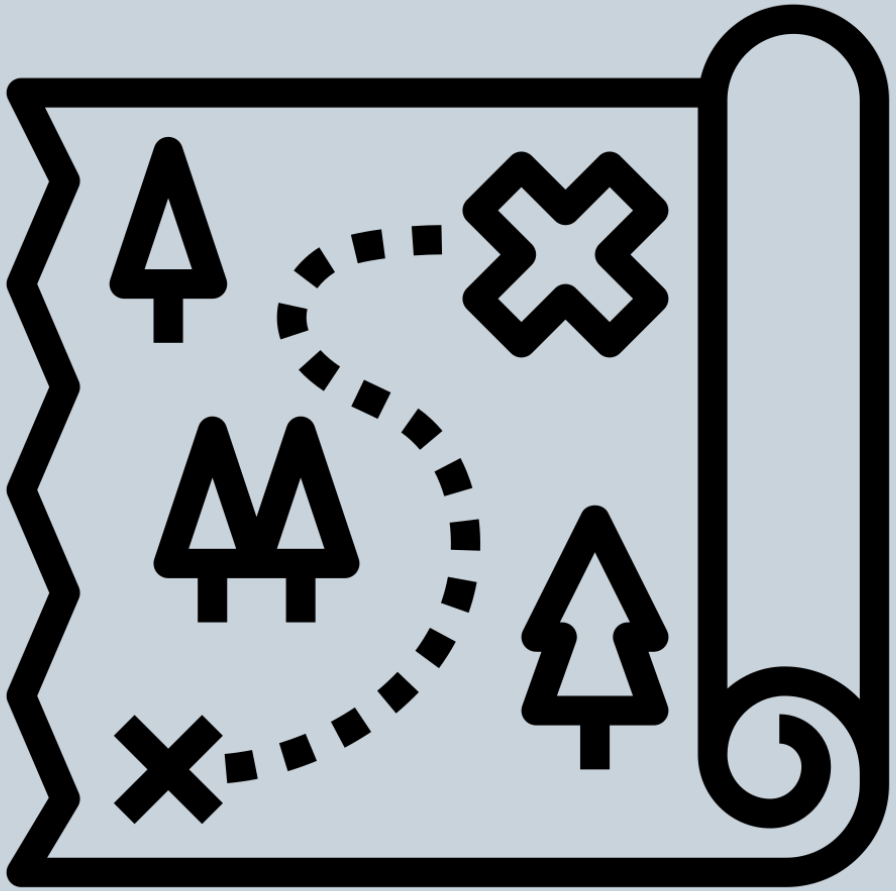
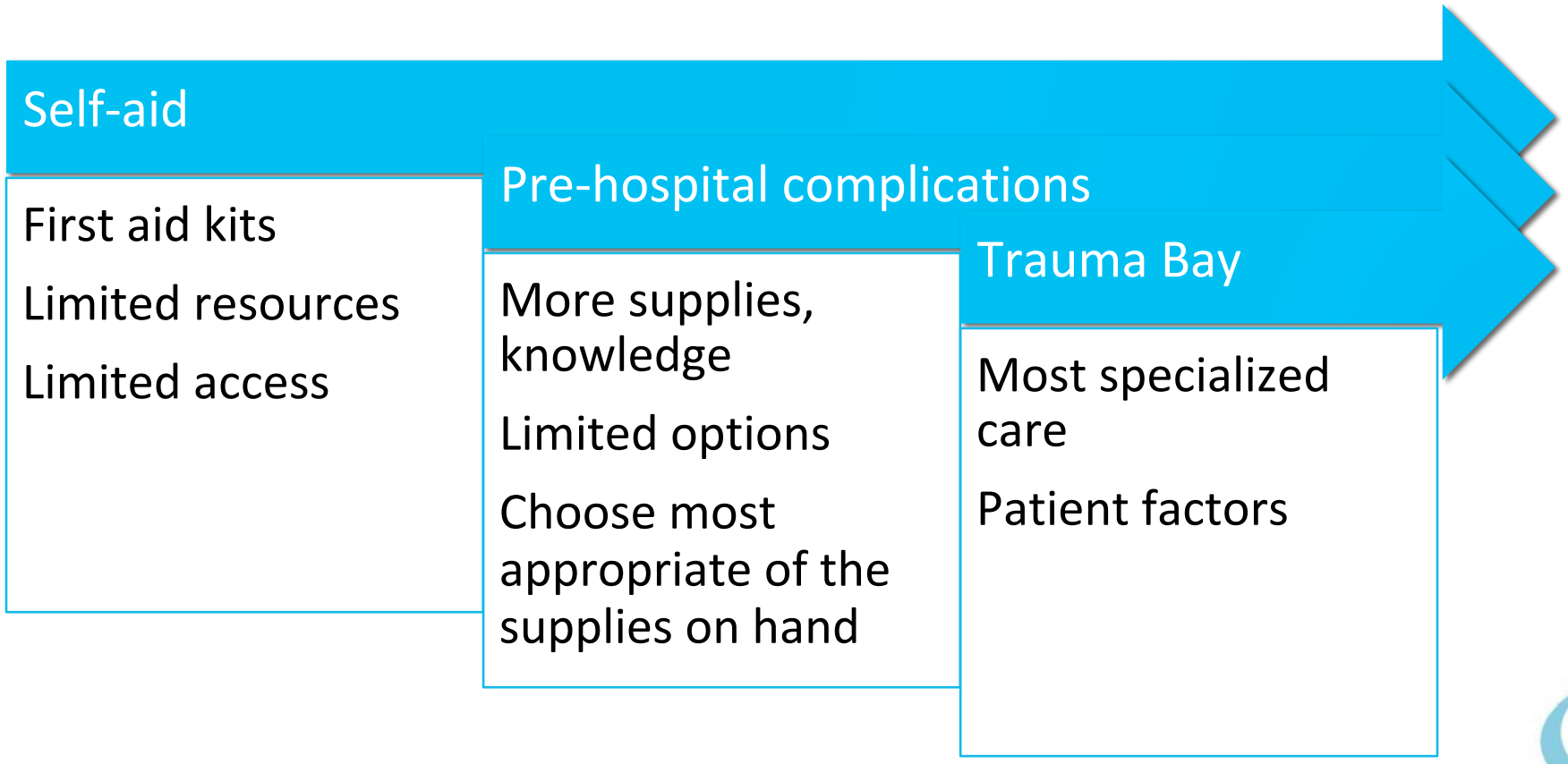


Let’s Review

Transitions of Care



Test Questions

Instructions:

Review questions and answers with attendees in whichever format you prefer. If you have multiple-choice questions, please use the Audience Response Cards that will be provided to attendees.

You MUST provide the correct answers to the attendees at this time. This is an ACPE requirement.

What transitions of care could a mountain rescue patient experience?

1) Initial Self-Care / Wilderness aid
2) Pre-hospital transport
   A) Ground transport
   B) Air transport
3) Hospital intake
   A) Trauma bay
   B) Emergency department
4) Inpatient
   A) Operating room
   B) Intensive Care
   C) Wards

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What is going on? What is the first thing he should do?

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What risk factors did Jack have for developing Acute Mountain Sickness?

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- Climbing at elevation > 2,500 m
  - Summit of King's Peak is 4125 m
- Non-acclimatized, altitude naïve
  - Austin, TX is 400m
- Symptoms started within 5 days of arrival to altitude
- LLSS of 6 = moderate AMS

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How do you choose to chemically restrain the patient?

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HEALTH-SYSTEM PHARMACISTS

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