Treatment Options for Frostbite: 

\textbf{tPA or Bust}

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PGY-2 Emergency Medicine Resident

Pharmacy Grand Rounds 
January 19, 2016
Objectives

- Explain the pathophysiology of frostbite
- Identify indications for different pharmacotherapy treatments of frostbite
- Outline a dosing strategy for tPA in the treatment of frostbite
What is the mechanism of injury surrounding frostbite?

A. Vasoconstriction  
B. Direct cellular damage  
C. Increased vascular permeability  
D. Thrombosis  
E. A & C  
F. All of the above
Which of the following is a recommended treatment modality for severe frostbite?

A. Corticosteroids & fluid restriction
B. Vasodilators & thrombolytics
C. Ibuprofen & thrombolytics
D. I have no idea
What is Frostbite?

- Freezing, cold, localized thermal injury
- Occurs when tissues are exposed to temperatures below their freezing point for a sustained period of time
Frostbite Times

NWS Windchill Chart

Wind Chill (°F) = 35.74 + 0.6215T - 35.75(V^{0.16}) + 0.4275T(V^{0.16})
Where, T= Air Temperature (°F) V= Wind Speed (mph)

Effective 11/01/01

http://www.thorntonweather.com
Epidemiology

- Historically found in soldiers
- Now seen in homeless patients in cold climates
- Recreational sports
- Men > Women
- Middle aged patients
- Industrial injury
  - Liquid Nitrogen
  - Freon Gas
  - Dry Ice

McIntosh et al. Wilderness Environ Med. 2014;25:S43-S54
Risk factors

- Absolute temperature
- Time of exposure
- Exposure to wind and moisture
- Extremes of age
- Patient comorbidities

<table>
<thead>
<tr>
<th>Alcohol Consumption</th>
<th>Psychiatric illness</th>
<th>Substance Abuse</th>
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</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>Raynaud’s Disease</td>
<td>Neuropathies</td>
</tr>
<tr>
<td>Smoking</td>
<td>Peripheral Vascular Disease</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>

Tissue Cooling Phases

- **Pre-Freeze**
  - Tissue cooling, Neuronal cooling

- **Freeze-Thaw**
  - Intracellular ice crystals (rapid onset freeze)
  - Extracellular ice crystals (slower freeze)
  - Protein and lipid derangements
  - Cellular electrolyte shifts → dehydration → lysis → death

- **Vascular Stasis**
  - Vasoconstriction & Vasodilation
  - Blood can leak from vessels or coagulate within them
  - Ischemia from thrombosis
  - Inflammation mediated by thromboxane, prostaglandins, bradykinins, histamine
  - Intermittent vasoconstriction with continued perfusion injury

- **Late Ischemia**
  - Ischemia from thrombosis
  - Inflammation mediated by thromboxane, prostaglandins, bradykinins, histamine

McIntosh et al. *Wilderness Environ Med.* 2014;25:S43-S54
Pathophysiology

- Hypothermia
- Inflammation
- Thrombosis
- Frostbite
- Damage

## Classification: Degree

<table>
<thead>
<tr>
<th>Degree</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Degree</td>
<td>Numbness and erythema&lt;br&gt;White/yellow, firm and raised plaque forms&lt;br&gt;No gross tissue infarction&lt;br&gt;Mild edema</td>
</tr>
<tr>
<td>Second Degree</td>
<td>Superficial vesiculation&lt;br&gt;Clear/milky fluid accumulation&lt;br&gt;Surrounding erythema and edema</td>
</tr>
<tr>
<td>Third Degree</td>
<td>Deep hemorrhagic blisters form&lt;br&gt;Injury down to dermal vascular plexus</td>
</tr>
<tr>
<td>Fourth Degree</td>
<td>Injury extends through the dermis with necrosis extending through the muscle to the bone</td>
</tr>
</tbody>
</table>

McIntosh et al. *Wilderness Environ Med*. 2014;25:S43-S54
Frostbite Severity

## Classification: Grade

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of initial lesion at day 0 after rewarming</td>
<td>Absence of initial lesion</td>
<td>Initial lesion on distal phalanx</td>
<td>Initial lesion on carpal/tarsal area</td>
</tr>
<tr>
<td>Bone scanning day 2</td>
<td>Useless</td>
<td>Hypo-fixation of radiotracer uptake area</td>
<td>Absence of uptake on the digit</td>
</tr>
<tr>
<td>Blisters day 2</td>
<td>Absence of blisters</td>
<td>Clear blisters</td>
<td>Hemorrhagic blisters on digit</td>
</tr>
<tr>
<td>Prognosis day 2</td>
<td>No amputation</td>
<td>Tissue amputation</td>
<td>Bone amputation of digit</td>
</tr>
<tr>
<td></td>
<td>No sequelae</td>
<td>Fingernail sequelae</td>
<td>Functional sequelae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potential systemic involvement</td>
</tr>
</tbody>
</table>

Treatment Considerations
Mr. JW

- 28yo male who was found down in a snowbank at 6am New Years Day. Last seen 11pm
- Ambient temp 5°F with wind chills to -20°F
- Patients right shoe was off and he had no gloves on
- Layer of ice surrounded his right foot
Pre-Hospital Care

• Move patient out of the wind and find shelter
• Remove boots, wet socks, gloves
• Avoid re-warming if there is potential for re-freezing
  • Passively warm if able
    • Warm water
    • Body heat
• Limit additional trauma to the area
  • Avoid rubbing area
  • Do not walk on frozen feet

Initial Hospital Care

- ABCs
- Treat underlying unstable comorbidities or trauma
- Re-warm patient’s core temperature to 35°C before re-warming frostbitten area
- Remove jewelry from extremities
- Re-hydration with warm IV/PO fluids
- Initiate transfer to burn center if needed

Re-Warming Extremities

- Whirlpool bath at 38°C (37-39) of water and antiseptic

- Timing
  - Tissue pliable & red/purple color
  - 30 minutes (10-60 minutes)

- Pain control
  - NSAID
  - Opioid

NSAID = Nonsteroidal anti-inflammatory drug
JW: Hospital Arrival

- Drowsy and slow to respond, core temp 31.3°C
- Right foot encased in ice, left was cold & soft, hands were cold and hard to palpation
- Given warm IV fluids, blankets, room temp increased to increase core temperature
- Right foot and hands rapidly re-warmed for 30 minutes in 37°C water bath
- Hemorrhagic blisters formed on all three extremities and doppler pulses absent in both hands
Angiography
Tc-99m Bone Scanning
Severe Frostbite
Investigated Pharmacotherapies

- Low Molecular Weight Dextran
- Vasodilators

<table>
<thead>
<tr>
<th>Iloprost</th>
<th>Nitroglycerin</th>
<th>Pentoxifylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandin E1</td>
<td>Nifedipine</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Buflomedil</td>
<td></td>
<td>Phenoxybenzamine</td>
</tr>
</tbody>
</table>

- Aspirin/Ibuprofen
- Heparin/LMWH
- Thrombolysis: tPA

LMWH: Low Molecular Weight Heparin
tPA: Tissue plasminogen activator

McIntosh et al. Wilderness Environ Med. 2014;25:S43-S54
Low Molecular Weight Dextran

- Intravenous LMWD shown to decrease blood viscosity → prevent RBC aggregation and thrombus formation
- Animal studies have shown mixed results
- Increased benefit if given early - in the field
- Risk for anaphylaxis
- No longer standard of care

LMWD = Low Molecular Weight Dextran

McIntosh et al. *Wilderness Environ Med.* 2014;25:S43-S54
Anti-inflammatory agents

- No trials demonstrating benefit of any particular agent
- Most evidence in animal models
- Heggers et al:
  - Topical aloe vera q6h + ibuprofen 12mg/kg/day PO + Penicillin
  - Amputation: 7% protocol vs. 32.7% control
- Ibuprofen 12mg/kg/day with max 2400mg/day
- Aspirin 250 mg daily has been studied

McIntosh et al. *Wilderness Environ Med.* 2014;25:S43-S54
Vasodilators

- Iloprost
- Prostaglandin E1
- Nitroglycerin
- Nifedipine
- Reserpine
- Buflomedil
- Phenoxybenzamine
- Pentoxyfylline
Iloprost Treatment: Groechenig

- Case series report on 5 patients
- 2\textsuperscript{nd} and 3\textsuperscript{rd} degree frostbite
- Iloprost 0.5 ng/kg increasing over 3 days to 2ng/kg for 14-42 days
  - Additional heparin + cortisone in one patient
- Pain relief in 1-3 days
- Perfusion improved
- No cases of amputation

Iloprost: Cauchy et al.

- Open label, randomized trial of 47 patients with stage 3-4 frostbite
- All patients received rapid re-warming to extremities + aspirin 250mg + Buflomedil 400mg IV

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Aspirin 250 mg QD + Buflomedil 400mg IV QD x 8 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 2</td>
<td>Aspirin 250 mg QD + iloprost 0.5-2ng/kg/min x 6h per day x 8 days</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Aspirin 250 mg QD + iloprost 0.5-2ng/kg/min x 6h per day x 8 days <strong>PLUS</strong> tPA 100 mg</td>
</tr>
</tbody>
</table>

Iloprost: Cauchy et al.

- More stage 4 lesions in tPA cohort
- Small patient group studied
- Iloprost and Buflomedil not available in the United States

<table>
<thead>
<tr>
<th>Group</th>
<th>At risk amputation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>39.5 %</td>
</tr>
<tr>
<td>Iloprost</td>
<td>0</td>
</tr>
<tr>
<td>Iloprost + tPA</td>
<td>3.1 %</td>
</tr>
</tbody>
</table>

Tissue Plasminogen Activator for Severe Frostbite

- Case series report from HCMC

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 18-75yo with severe frostbite</td>
<td>1. Severe hypertension</td>
</tr>
<tr>
<td>2. No improvement with rewarming</td>
<td>2. Recent trauma/stroke/bleeding condition</td>
</tr>
<tr>
<td>3. Absent doppler pulses in limbs</td>
<td>3. Pregnancy</td>
</tr>
<tr>
<td>4. No perfusion on Tc-99m scan</td>
<td>4. Mental incapacity</td>
</tr>
<tr>
<td></td>
<td>5. Drug/alcohol intoxication</td>
</tr>
<tr>
<td></td>
<td>6. Repeated freeze-thaw cycle</td>
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<tr>
<td></td>
<td>7. &gt;48h cold exposure</td>
</tr>
</tbody>
</table>

HCMC = Hennepin County Medical Center

Dosing protocols

• 1989-94: intraarterial tPA
  • 0.075mg/kg/hr x 6 hours, re-angio, repeat tPA
• 1995-97: intravenous tPA
  • multiple dosing strategies
• 1997-2003: intravenous tPA
  • 0.15mg/kg bolus followed by 0.15mg/kg/hr with max
    100 mg or for 6 hours
• Heparin given following tPA conclusion
• Warfarin started 3-5 days after heparin started, continuing for 4 weeks

Outcomes

- Control patients: all digits with absent flow on Tc-99m scans were amputated

- tPA patients
  - 174 digits at risk
  - 33 amputated (19%)

- Complications
  - 2 patients with bleeding complications
  - IA patients: bleeding at arterial line site and hematuria

Thrombolytic protocol

- IV tPA 0.15mg/kg bolus + 0.15mg/kg/hr infusion
  - Max 100 mg or 6 hours of infusion
- IV UFH titrated to PTT 2x control starting after completion x 3-5 days
- Warfarin starting day 3-5 for a total of 2-4 weeks
- Pain management with narcotics
- Ibuprofen 400-600mg QID
- Light dressings with topical antimicrobials

Additional HCMC data

- Retrospective review of 11 patients (2008-10)
- Same IV tPA and heparin protocol as previous study
- 16 hands and 6 feed affected
- 73 digits with absent perfusion on Tc-99m scan
- 43 digits required amputation (59%)

Johnson AR et al. *Foot Ankle Spec.* 2011;4:344-8
University of Utah Experience

- Retrospective case-control study
- tPA protocol vs. controls (historical and concurrent)
- Intraarterial tPA: 0.5 to 1 mg/h + UFH 500 units/hr
- Repeat angiograms every 8-12 hours and continue tPA until perfusion restored or 48h

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>tPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit amputations</td>
<td>97/234 (41%)</td>
<td>6/59 (10%)</td>
</tr>
<tr>
<td>Proximal amputations</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

University of Utah Protocol

1. Placement of catheter into Brachial or Femoral artery
2. tPA bolus 2-4 mg IA
3. Administration of tPA 1mg/hr IA (dose divided by # of extremities)
4. CBC, platelets, fibrinogen, PTT every 6 hours
   - Discontinue tPA for fibrinogen <150mg/dL
5. Repeat angiography at 12 hours (and 24 hours if deficit persists)
   - Discontinue tPA with documented reperfusion (total time not >24 hours)

References:
Regions Hospital Experience

- Retrospective, observational cohort study
- Intrarterial thrombolysis + heparin
  - Urokinase + papaverine
  - tPA 1mg/hr + papaverine
  - Reteplase 0.15 to 05 mg/hr
  - Tenecteplase 0.25 – 0.5 mg/hr
- Repeat angiography every 24 hours
- Thrombolysis continued until reperfusion or 72h
Regions Hospital Experience

- 62 patients received IA thrombolysis
- 472 digits were at risk
- 148 digits required amputation (31.3% rate)

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th># Amputated/ # at Risk</th>
<th>Percentage Salvaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full responder</td>
<td>0/279</td>
<td>100%</td>
</tr>
<tr>
<td>Partial responder</td>
<td>83/128 (65%)</td>
<td>35%</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>65/65 (100%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Gonzaga T. J Burn Care Res. 2015
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Duration Max (h)</th>
<th>No. of patients</th>
<th>No. at risk digits</th>
<th>No. amps</th>
<th>% at risk amputations</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td><strong>SLC UT</strong></td>
<td>48</td>
<td>7</td>
<td>65</td>
<td>12</td>
<td>18.5%</td>
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<tr>
<td></td>
<td>Retro</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>St. Paul</strong></td>
<td>72</td>
<td>62</td>
<td>472</td>
<td>148</td>
<td>31%</td>
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<tr>
<td></td>
<td>Retro</td>
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</tr>
<tr>
<td></td>
<td><strong>Boston</strong></td>
<td>36</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Case report</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td><strong>Burlington</strong></td>
<td>24</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0%</td>
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<td>Case report</td>
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<tr>
<td></td>
<td><strong>Ann Arbor</strong></td>
<td>20</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>0%</td>
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<tr>
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<td>Case report</td>
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<td></td>
</tr>
<tr>
<td>Venous</td>
<td><strong>France</strong></td>
<td>24</td>
<td>16</td>
<td>159</td>
<td>5</td>
<td>3.1%</td>
</tr>
<tr>
<td></td>
<td>Pro/Rand</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Minneapolis</strong></td>
<td>8</td>
<td>11</td>
<td>73</td>
<td>43</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>Retro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA or IV</td>
<td><strong>Minneapolis</strong></td>
<td>IA: NA</td>
<td>IA: 6</td>
<td>174</td>
<td>33</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>Retro</td>
<td>IV: 12</td>
<td>IV: 13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>118</td>
<td>966</td>
<td>241</td>
<td>25%</td>
<td>9 (8%)</td>
</tr>
</tbody>
</table>
**tPA Contraindications**

- Recent trauma
- Recent surgery or hemorrhage
- Bleeding diathesis
- Uncontrolled hypertension
- Pregnancy
- Evidence of freeze-thaw-refreeze injury
- Prolonged cold exposure (>24 hours)
- >24 hours since rewarming
- *Neurologic impairment/ETOH/Drug use

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Johnson AR et al. *Foot Ankle Spec*. 2011;4:344-8

Gonzaga T. *J Burn Care Res*. 2015
Anticoagulation

• Unfractionated heparin studied early in the treatment of frostbite
  • Mixed results in animal studies
  • Not been shown to be efficacious on its own
• Use limited to combination with thrombolysis
• Long-term anticoagulation has not been studied other than protocols from tPA studies
  • 4 weeks LMWH vs. warfarin post tPA
  • Some protocols use antiplatelet agents

McIntosh et al. Wilderness Environ Med. 2014;25:S43-S54
Wound care

• Blister Debridement
  • Consider for clear blisters
  • Avoid in hemorrhagic blisters
• Aloe Vera gel
  • Apply to warmed extremities with wound changes every 6 hours
• Loose, dry gauze dressings can be applied
• Hyperbaric oxygen

What would your recommend for JW?

A. Supportive treatment and fentanyl 100mcg IV push q1h for pain
B. iloprost 0.5-2ng/kg/min x 6h per day x 8 days
C. tPA 0.9mg/kg IV. 10% given as bolus, 90% over 1 hour
D. tPA 0.5mg/hr IA in each arm + heparin 500 units/hr
JW follow-up
**Treatment Pathway**

**Re-warm extremities**

- Doppler pulses
  - Yes
  - **Imaging**
    - Perfusion
      - Absent perfusion
        - **Administer tPA + heparin**
          - **IV:** 0.15mg/kg bolus + 0.15 mg/kg/hr x 6h (max 100mg) followed by IV heparin
          - **IA:** 1mg/hr total (split between limbs) until perfusion returns + 500 IU/hr heparin
        - No contraindications

- No

**Supportive treatment**
- Topical aloe vera gel
- Light dressings
- Ibuprofen 12mg/kg/day
- Opioids for pain control
Treatment Options for Frostbite: tPA or Bust

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January 19, 2016