Alaska Acute Frostbite Management Guidelines

FROSTBITE CARE IN ALASKA 2024

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Drawing in large part from, and with credit to, all those who developed:
Alaska Cold Injury Guidelines
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Division of Public Health
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Other references included at end of document.

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Alaska Acute Frostbite Management Guidelines

Purpose

To revise Alaska treatment guidelines for frostbite of the extremities; to encourage treating teams to consider early expert consultation, transfer as necessary, enable early access to systemic thrombolytics for eligible patients, and to standardize care across the state.

Background and Scope

The State of Alaska has an over 25-year history of producing guidelines for the treatment of cold injuries. In June of 2023 an ad hoc committee convened to review the initial management of frostbite. The committee was composed of members from the Trauma Systems Review Committee, members from the Alaska Chapter of the American College of Emergency Physicians, local vascular surgeons, and military physicians. Systemic hypothermia, avalanche burial, submersion and immersion injury are outside the scope of this document.

Epidemiology

The Alaska Trauma Registry was queried for cold-related injuries with a mechanism of natural or environmental causes that required hospitalization within Alaska. A five-year period from 2018-2022 was selected with the intent of capturing Alaska's most severe and recent cases of frostbite. 240 patients were identified from this time-period as having frostbite-specific injuries that required hospitalization. Of the sample, 167 cases identified as male (69.6%) and 73 cases identified as female (30.4%), with the average age of a case being 42.8 years. Most cases were either Alaska Native/American Indian (100, 41.7%) or Caucasian/White (99, 41.3%), and nearly 30% of all cases (63) were identified as being individuals experiencing homelessness. From the time-period, severe frostbite injuries had a mortality rate of 5.00% (12/240), most often from a correlative and additional diagnosis of hypothermia. Out of the frostbite cases that did require hospitalization, a majority were admitted and cared for by hospitalists and intensivists (68.5%), although other subspecialities such as trauma, orthopedics and vascular surgery did admit these patients as well. Overall, this patient population had an injury severity score (ISS) of 7, and were predominantly discharged home after their hospital stay (150, 62.5%). However, prior to a final discharge, 47 (19.5%) cases were transferred to a larger trauma center for higher levels of care, with 1 requiring transfer out-of-state. It is important to note that the sample of 238 cases does not capture every severe frostbite injury throughout the Alaska. The Alaska Trauma Registry will not capture individuals who sustain frostbite injuries and pass away from their injuries prior to

receiving care, those treated in clinics or emergency departments not requiring admission, or those who are assumed to never seek care for their injuries. We recognize the number of 238 cases from 2018-2022 to be an underestimate of the burden of severe frostbite within Alaska.

Use of Thrombolytics

Thrombolytics have been used in the acute management of frostbite as an active treatment to limit injury during reperfusion. Alteplase (tPA) more commonly and now additionally tenecteplase (TNKase) have been used in the United States to treat acute frostbite as an off-label use. Although data is somewhat limited due to the variability of protocols and the rarity of this disease, thrombolytics have become standard of care by burn centers and are now endorsed by the American Burn Association and the Wilderness Medical Society. Evidence suggests a benefit to early administration of thrombolytics. Patients with severe frostbite of the extremity may be a candidate for administration of thrombolytics. Based on available literature and clinical experience of this working group, these guidelines recommend thrombolytics to be administered within 24 hours from rewarming. To note, contraindications prohibit use after 48 hours; cases within this intermediate window will require best judgment from clinical providers. A frostbite injury of the extremities subset of 58 patients from the Alaska Native Medical Center (ANMC) trauma registry was further analyzed during the same period, 2018 - 2022. ANMC tracks tissue plasminogen activator (tPA) use in their registry, which is not currently available in the statewide cold injury data set. Routine intravenous tPA use per local guidelines began in the year 2017. A total of 21 patients received systemic tPA during this period, representing 36.2% of the admitted cases. The ANMC experience was like previously published studies revealing a reduction in the need for amputation of any level. Six (28.5%) of the patients who received tPA required amputations in comparison to 27 patients (46.6%) of the total group and 21 patients of the 39 in the group who did not receive tPA (53.8%). One major adverse bleeding event occurred, related to a gastrointestinal bleed. Thrombolytics can be administered systemically or intra-arterial via catheter directed therapy. There have been no direct comparison studies to suggest superiority of one administration method over the other. *Based on the rural and remote geography of Alaska and the distance to definitive care, these recommendations support systemic administration of thrombolytics.* Some treatment guidelines suggest use of advanced imaging modalities (i.e. angiography or nuclear imaging with technetium-99m scanning) to help in

assessment and medical therapy decision making. However, these are not routinely available in Alaska and would further delay access to therapy and are thus not recommended. *Clinical assessment by an experienced provider is sufficient to determine the need for thrombolytics. Consultation (telehealth preferred if available) is recommended if needed to support local providers' decision to initiate treatment or transfer.*

Transfer and Definitive Care

The Level II Trauma center at ANMC continues collaboration with the UW Medicine Regional Burn Center at Harborview Medical Center for treatment of thermal injuries. Harborview Medical Center is the closest American Burn Association-verified Regional Burn Center for Alaska. ANMC has a trained burn surgeon and the many ancillary services required to provide quality thermal injury care. The collaboration between these two centers has permitted some thermal injuries to receive care in Alaska. Additional Alaska trauma centers have a commitment to cold injuries and some patients may safely be treated locally. **Alaskan hospitals that are able to provide definitive care for severe frostbite should have the ability to perform rapid rewarming and deliver systemic thrombolytics, capability to stabilize and treat other concomitant injuries, which may include systemic hypothermia or trauma-related injuries, and intensive care units.** Usual referring patterns should be utilized when transfer is required.

Clinical Management Guidelines

Out of Hospital and Rural Clinic Treatment.

Like other traumatic injuries the priority in cold injury is to assess for and stabilize immediate life threats. Frostbite is a localized cold injury and in the setting of systemic cold injury (unintentional hypothermia) or other traumatic injuries, is often not the initial priority. After life threats have been stabilized, initial treatment of frostbite includes removal from the cold environment. Most frostbite injuries affect the extremities, but other areas of the body may be affected, such as face (ears and nose most commonly), trunk, or genitalia. Thermal injuries to these areas require specialist consultation and are outside the purview of this document.

When not possible to begin and maintain warming measures consideration should be given to delayed rewarming. Repeated freezing and thawing have been shown to increase tissue injury. If transport times from field extraction is expected to be less than 2 hours, it is reasonable to keep the extremity frozen until rapid re-warming can be performed at a clinic or hospital setting. Any duration of transport beyond this timeframe typically results in passive warming and thus, active rewarming measures are preferred. Elevation of the affected extremities and minimal mechanical handling is recommended during transport and initial care of frostbite injuries.

Initial Treatment, Assessment and Grading of Injury- ALL PATIENTS

- Treatment of hypothermia and medical / traumatic emergencies take priority.
- Remove any tight-fitting clothing or jewelry.
- Let skin area dry passively.
- Avoid rubbing or massaging the injured skin to prevent soft tissue injury.
- Immersion of the extremity in warmed water (37-39°C) is the preferred method for rewarming.
    - Add chlorhexidine or povidone-iodine when available.
    - Any facility with warm, running water will have the capability to achieve rapid rewarming by replenishing warm water in a basin. A thermometer to measure water temperature may be helpful.
    - Consider using a whirlpool or sous vide if available.
    - Continue until tissue becomes red in color (flushed) or soft and pliable (typically 20-40 minutes).
- After rewarming is complete, grade the level of soft tissue injury. **(Appendix D)**
    - Photo documentation and the use of standard attached form is recommended.
    - Assess for eligibility for thrombolytics:
        - Clinical evaluation reveals grade 3 or 4 extremity frostbite
        - No contraindications identified for candidacy
        - Telehealth consult may be used to help grade severity
- Analgesia during rewarming will likely be required.
    - Non-steroidal anti-inflammatory drugs (i.e. ibuprofen, naproxen, ketorolac).
    - Utilize opioids or other pain modalities as needed.

    - A peripheral nerve block may be considered when available and when procedure does not significantly delay warming. Follow local protocols for use of blocks in patients who may be candidates for thrombolytics.
- Verify tetanus status and update if greater than 5 years from last booster.
- If transfer is required for definitive care, contact definitive care site.
    - Initiation of thrombolytics may be recommended.
    - Thrombolysis is not a contraindication to Air Medical transport and has been safely administered during flight.
- Apply a dry, loose bulky dressing. Separate digits gently with gauze.
    - If transport is delayed, initial blister care may be initiated under the guidance of the accepting facility's specialist.

SUPERFICIAL Injury / GRADE 1-2

- Many superficial cold injuries may safely be discharged:
    - Consider these questions prior to disposition.
        - Is pain adequately controlled?
        - Is the patient able to perform wound care?
        - Does the injury limit the ability to perform activities of daily living?
        - Does the patient have adequate support system?
        - Does the patient have a safe discharge disposition?
- Wound care performed or directed by appropriate consulting teams:
    - Grade 1 injuries without blisters can be left open to air and do not require wound care or dressings.
    - Grade 2 injuries with clear blisters may be considered for debridement if they are larger than 2cm or impair range of motion. Topical antimicrobial ointment can then be applied and non-stick dressing or greasy gauze placed.
    - If debridement occurs, apply a lightly padded dressing, in a position of function. Place dressing in between digits to separate.
- Arrange for appropriate local follow-up with primary care, wound care, or surgical specialty follow up as appropriate and available.
- Recommend avoidance of tobacco products.
- Injury prevention is recommended as re-injury is common:
    - Limit time outdoors in cold, wet or windy weather.
    - Dress in several layers of loose, warm clothing.

- Wear socks and sock liners that fit well, wick moisture and provide insulation.

Definitive Care Site Inpatient Treatment – SUPERFICIAL Injury (GRADE 1-2) requiring admission or DEEP Injury (GRADE 3-4)

- Establish IV access.
- Obtain basic labs as appropriate, which may include CBC, BMP, INR, PTT.
- Encourage oral hydration or consider warm crystalloid infusion.
- Routine antimicrobials are not indicated.
- Wound care performed or directed by appropriate consulting teams:
  - Leave hemorrhagic blisters intact.
  - Apply topicals to intact blisters daily. This may include aloe vera or an iodine-based topical.
- Apply a lightly padded dressing, in a position of function. Place dressing in between digits to separate.
- Consider splinting to prevent additional trauma to damaged tissue. Therapy consults (PT/OT) may assist in range of motion or splinting as needed.
- Elevate affect body parts. Early avoidance of ambulation on thawed lower extremities (unless only distal toes are affected) may be utilized, but weight bearing as tolerated should be initiated by 72 hours.
- Ibuprofen 400mg Q6hrs or naproxen 220mg Q12hrs for 7 days, unless contraindicated (i.e. initiation of thrombolytic therapy).
- Use multi-modal pain management strategies, including neuropathic pain treatments.
- Consider weaning of narcotics as soon as practical. Long-term use of narcotics is typically not required in frostbite injury.

DEEP INJURY / GRADE 3 - 4 (If less than 24 hours since rewarming and not receiving active treatment for systemic hypothermia)

- Initiate thrombolytic therapy as quickly as possible.
  - Consider obtaining two IV access sites and complete any invasive or semi-invasive procedures prior to administration of thrombolytics (e.g. IV starts, Foley catheter, NG tube, etc.).
  - Obtain actual patient weight.
  - Review **Thrombolytic Contraindications (Appendix B).**
  - Obtain consent.

- Initiate infusion **(see Appendix C: Thrombolytic Administration Instructions)**.
- Thrombolytics have been safely used in pediatric patients. Recommend consultation with pediatric pharmacist for dosing if age less than 5 years.
- Admit to monitored care (continuous telemetry and hourly nursing assessments for neurochecks) for 24 hours post-thrombotic therapy to monitor for hemorrhage and angioedema.

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Appendix A: Clinical Frostbite Management Algorithm

Initiate rapid rewarming for acute extremity frostbite with 37-39°C water for 20-40 mins or until skin red in color or soft and pliable (consider sous vide or whirlpool)

Assessment for severity of frostbite after rewarming (Grade I-4). See figure below

Superficial (Grade 1-2)

- Topical ointment and clean dressings daily
- NSAIDs
- Elevation of affected parts
- Avoid tobacco
- Tetanus-diphtheria immunization

Deep (Grade 3-4)

Has it been less than 24 hours since rewarming?

No

Yes

Thrombolytics and admit / transfer to monitored care (if not contraindicated)

Admit

Is the follow discharge criteria met?

- Pain is controlled
- Ability to perform wound care
- Perform activities of daily living
- Adequate support system
- Safe discharge disposition

No

Yes

Discharge with appropriate follow up

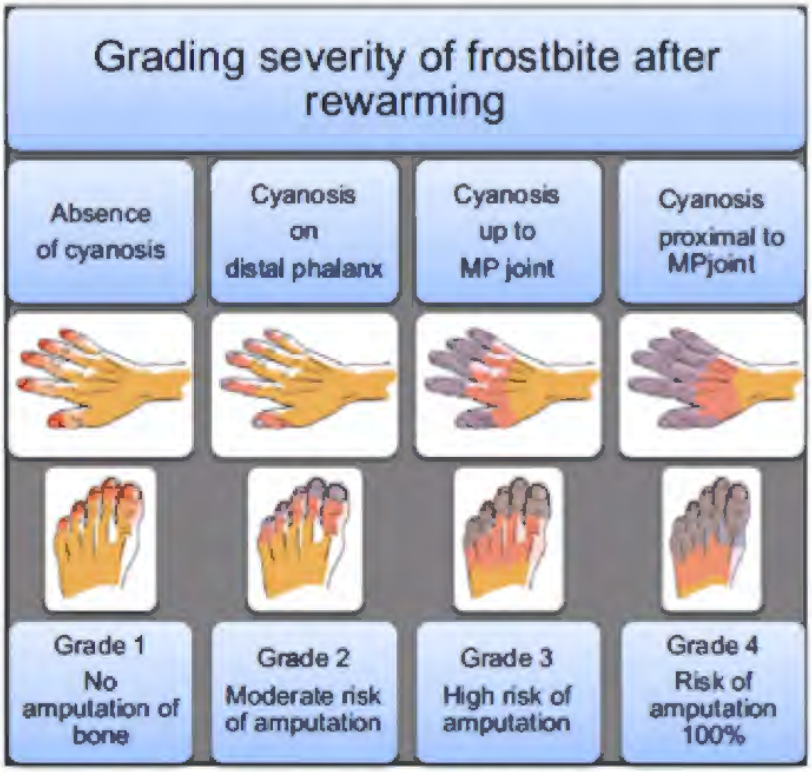
Thrombolytic Contraindications

Absolute

- History of intracranial hemorrhage
- History of ischemic stroke, closed head trauma, or intracranial / intraspinal surgery within the previous 3 months
- Known intracranial arteriovenous malformation, neoplasm, or aneurysm
- Active bleeding, with the exception of menses
- Uncontrolled hypertension at presentation (>180/110mmHg) that does not respond to treatment
- Inability to obtain history or consent
- Known bleeding diathesis

Relative

- Traumatic or prolonged (>10 min) CPR
- Major surgery or serious non-head trauma in the previous 14 days
- History of GI bleed in the previous 21 days
- Recent arterial puncture at a noncompressible site
- Pregnancy
- Myocardial infarction within the previous 3 months
- Recent lumbar puncture
- Multiple freeze thaw cycles



Source: Cauchy E. et al, Wild & Env Med 27, 92-99 (2016)

Approved by Alaska Trauma Systems Review Committee on 2/21/2024.

Alaska Frostbite Care Guidelines

1. Initiate rapid rewarming for acute extremity frostbite with 37-39°C water for 20-40 minutes or until skin red in color or soft and pliable (consider sous vide or whirlpool).
2. Assessment for severity of frostbite after rewarming (Grade 1-4). Refer to 11.
    a. If superficial (Grade 1-2), jump to 3
    b. If deep (Grade 3-4) jump to 4
3. Superficial (Grade 1-2)
    a. Topical ointment and clean
    b. NSAIDs
    c. Elevation of affected parts
    d. Avoid tobacco
    e. Tetanus-diphtheria immunization
    f. Jump to 5
4. Deep (Grade 3-4)
    a. Has it been less than 24 hours since rewarming?
        i. If no, jump to 5
        ii. If yes, jump to 6
5. Are the following discharge criteria met?
    a. Pain is controlled
    b. Ability to perform wound care
    c. Ability to perform activities of daily living
    d. Adequate support system
    e. Safe discharge disposition
    f. If yes to all of the above, jump to 7
    g. If no to any of the above, jump to 8
6. Thrombolytics and admit/transfer to monitored care (if not contraindicated)
7. Discharge with appropriate follow up
8. Admit

Thrombolytic Contraindications

1. Absolute
    a. History of intracranial hemorrhage
    b. History of stroke, closed head trauma, or intracranial/intraspinal surgery within the previous 3 months
    c. Known intracranial arteriovenous malformation, neoplasm, or aneurysm
    d. Active bleeding, with the exception of menses
    e. Uncontrolled hypertension at presentation (>180/110 mm/hg) that does not respond to treatment
    f. Inability to obtain history or consent
    g. Known bleeding diathesis
2. Relative
    a. Traumatic or prolonged (>10 min) CPR
    b. Major surgery or serious non-head trauma in the previous 14 days

c. History of GI bleed in the previous 21 days
d. Recent arterial puncture at a noncompressible site
e. Pregnancy
f. Myocardial infarction within the previous 3 months
g. Recent lumbar puncture
h. Multiple freeze thaw cycles

Grading severity of frostbite after rewarming

1. Grade 1
    a. Absence of cyanosis
    b. No amputation of bone
2. Grade 2
    a. Cyanosis on distal phalanx
    b. Moderate risk of amputation
3. Grade 3
    a. Cyanosis up to MP joint
    b. Risk of amputation 100%

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Appendix B: Thrombolytic Contraindications

Absolute Contraindications:

- More than 48 hours from time of rewarming
- Acute systemic hypothermia being actively treated
- History of any intracranial hemorrhage
- History of ischemic stroke, significant closed-head or facial trauma, intracranial or intraspinal surgery within the previous 3 months
- Known intracranial arteriovenous malformation, neoplasm, or aneurysm
- Active bleeding, with the exception of menses
- Uncontrolled hypertension at presentation (blood pressure greater than 180 mmHg systolic and/or 110 mmHg diastolic) that does not respond to emergent treatment
- Inability to obtain history or consent due to altered mental status
- Known bleeding diathesis, including but not limited to:
    - Platelet count <100,000K
    - Heparin administration with elevated PTT
    - Current use of warfarin with INR>1.7
    - Current use of direct thrombin inhibitors or direct factor Xa inhibitors

Relative Contraindications:

- Traumatic or prolonged (>10 min) CPR
- Major surgery or serious non-head trauma in the previous 14 days
- History of gastrointestinal or urinary tract hemorrhage in the previous 21 days
- Recent arterial puncture at a noncompressible site
- Pregnancy
- Myocardial infarction within the previous 3 months
- Recent lumbar puncture
- Significant concurrent trauma

Multiple freeze thaw cycles

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Appendix C: Thrombolytic Administration Instructions

TNKase:

- Tenecteplase: 0.25 mg/kg intraVENOUS bolus
- Maximum dose of 25 mg

OR

Alteplase:

- **Bolus:** Alteplase 0.15mg/kg intraVENOUS over 15 minutes
- **Infusion:** Alteplase 0.15mg/kg/hour intraVENOUS for 6 hours
- Maximum total dose (including bolus) = 100mg

PLUS

Recommendation for therapeutic anti-coagulation for 72 hours after thrombolytic therapy is completed. This should follow local protocols and may be initiated with subcutaneous enoxaparin, intravenous heparin, or direct oral anti-coagulant therapy. There is little data to support anti-coagulation therapy beyond this period, although some institutions will initiate aspirin or other anti-coagulant therapy for up to four weeks.

Enoxaparin:

- Give enoxaparin promptly after completion of TNKase bolus OR alteplase infusion:
- eGFR of 30mL/min OR GREATER:
    - LESS THAN 75 years of age:
        - Enoxaparin 1 mg/kg subCUTANEOUS every 12 hours for 72 hours.
    - GREATER THAN 75 years of age:
        - Enoxaparin (0.75 mg/kg) subCUTANEOUS every 12 hours for 72 hours.
- GFR LESS than 30mL/min:
    - LESS THAN 75 years of age:
        - Enoxaparin 1 mg/kg subCUTANEOUS every 24 hours for 72 hours.
    - GREATER THAN 75 years of age:
        - Enoxaparin 1 mg/kg subCUTANEOUS every 24 hours for 72 hours.

OR

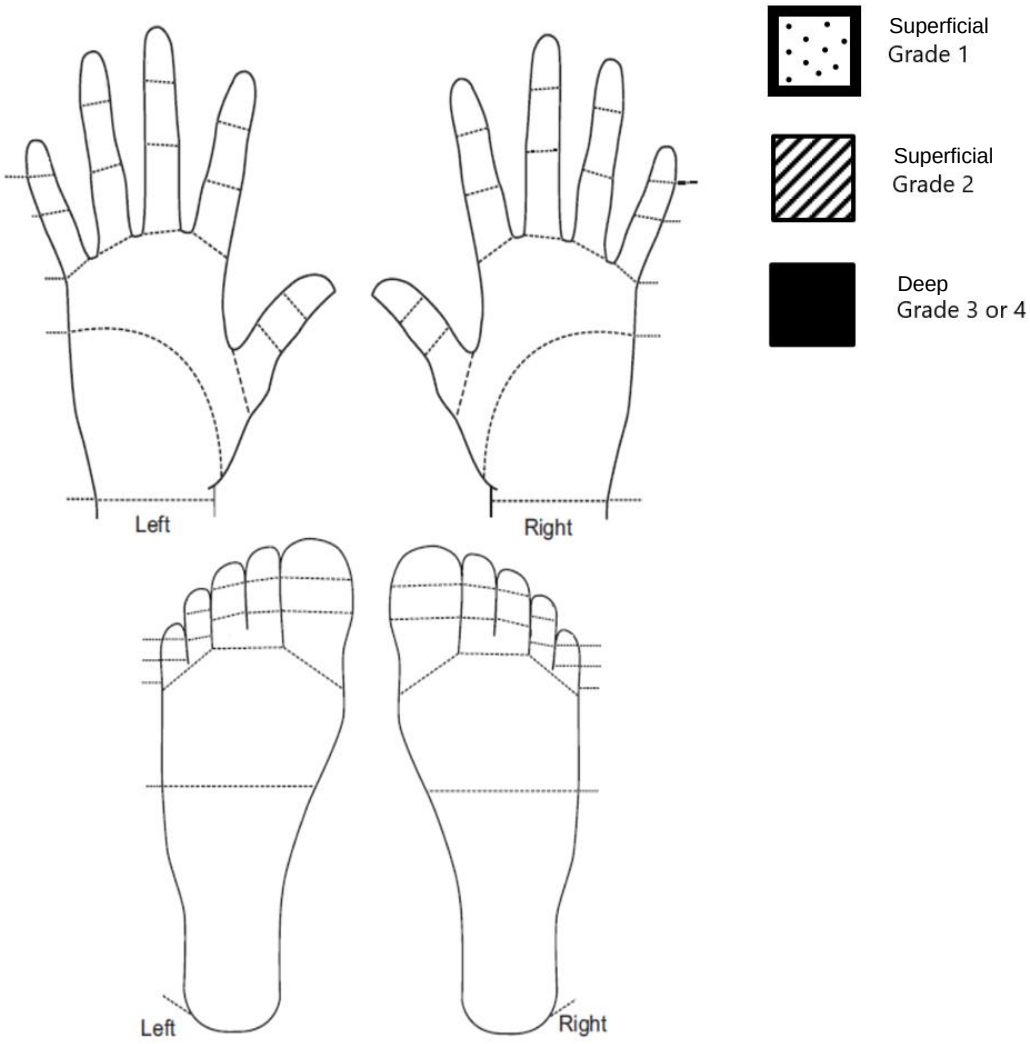
Heparin:

- Given heparin bolus promptly after completion of TNKase bolus OR alteplase infusion:
- Bolus: 80 units/kg, intraVENOUS bolus
- Followed by standard infusion rate to maintain anticoagulation target based on institutional protocol.

Appendix D: Grading of Frostbite Injury

FROSTBITE PROTOCOL
QUANTIFICATION OF FROSTBITE INJURY

- Mark with a dark pen the extent of the injury after rewarming. Note skin changes and indicate any evidence of cyanosis and hemorrhagic blisters.
- This sheet can also be used to monitor progress and change



DATE: _____ **TIME:** _____

PHYSICIAN'S NAME: _____ **PHYSICIAN'S SIGNATURE:** _____

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Appendix E: Sample Consent for Thrombolytics

The following is an example of verbiage that may be used in consenting patients for thrombolytic treatment for frostbite. Usual local approval process should be utilized prior to using this form.

Thrombolytic Consent for Treatment of Frostbite Extremity Injury

You have been diagnosed with severe (grade 3 or 4) frostbite. This is a serious condition and you are at high risk for amputation of some or all of the affected body part(s). This can result in long term disability.

Thrombolytics (alteplase and tenecteplase) are a type of medication that break up blood clots in the body. They are commonly used in strokes. Frostbite is known to cause blood clots in injured body parts. There are small studies that show that people with severe frostbite **may** be less likely to get amputations when they are given thrombolytic medications through an IV. The use of these medications is considered experimental and "off-label" by the Food and Drug Administration (FDA).

There are risks associated with this medication. The primary concern is the risk of causing serious bleeding elsewhere in your body such as in your chest, aorta, gastrointestinal tract, brain, or other location. There are certain conditions which could worsen and become life threatening with this medication, however based on screening those conditions are not considered likely by your physician. Allergic or other medication reaction, permanent disability, and even death can result from alteplase or tenecteplase.

No guarantee is given about the results or outcome of receiving this medication.

You are invited and encouraged to ask any questions you may have. You acknowledge that your questions have been answered to your satisfaction. You indicate that you understand that you may refuse this medication and may withdraw your consent at any time.

By your signature below you indicate that you understand this treatment, the risks and potential benefits, that you agree to receive it, and that you have read and understand this consent form.

Patient's Signature or Legal Representative				Date	Time
Relationship to Patient			Interpreter, If Utilized	Date	Time
Witness Signature	Date	Time	If Telephone Consent, Second Witness	Date	Time
Physician's Signature				Date	Time

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References:

1. Wibbenmeyer L, Lacey AM, Endorf FW, et al. American Burn Association Clinical Practice Guidelines on the Treatment of Severe Frostbite. Journal of Burn Care and Resuscitation. 2023 Apr 13:irad022. doi: 10.1093/jbcr/irad022. Epub ahead of print. PMID: 37045447.

2. Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. Wilderness Environ Med. 2001 Winter;12(4):248-55. doi: 10.1580/1080-6032(2001)012[0248:rsocos]2.0.co;2. PMID: 11769921.

3. McIntosh SE, Hamonko M, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, Giesbrecht G, McDevitt M, Imray CH, Johnson E, Dow J, Hackett PH; Wilderness Medical Society. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite. Wilderness Environ Med. 2011 Jun;22(2):156-66. doi: 10.1016/j.wem.2011.03.003. PMID: 21664561.

4. Handford C, Buxton P, Russell K, Imray CE, McIntosh SE, Freer L, Cochran A, Imray CH. Frostbite: a practical approach to hospital management. Extrem Physiol Med. 2014 Apr 22;3:7. doi: 10.1186/2046-7648-3-7. PMID: 24764516; PMCID: PMC3994495.

5. Millet JD, Brown RK, Levi B, Kraft CT, Jacobson JA, Gross MD, Wong KK. Frostbite: Spectrum of Imaging Findings and Guidelines for Management. Radiographics. 2016 Nov-Dec;36(7):2154-2169. doi: 10.1148/rg.2016160045. Epub 2016 Aug 5. PMID: 27494386; PMCID: PMC5131839.

6. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, Giesbrecht GG, McDevitt M, Imray CH, Johnson EL, Pandey P, Dow J, Hackett PH. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite: 2019 Update. Wilderness Environ Med. 2019 Dec;30(4S):S19-S32. doi: 10.1016/j.wem.2019.05.002. Epub 2019 Jul 17. PMID: 31326282.

7. Knapik JJ, Reynolds KL, Castellani JW. Frostbite: Pathophysiology, Epidemiology, Diagnosis, Treatment, and Prevention. J Spec Oper Med. 2020 Winter;20(4):123-135. doi: 10.55460/PDX9-BG8G. PMID: 33320326.

8. Joshi K, Goyary D, Mazumder B, Chattopadhyay P, Chakraborty R, Bhutia YD, Karmakar S, Dwivedi SK. Frostbite: Current status and advancements in therapeutics. J Therm Biol. 2020 Oct;93:102716. doi: 10.1016/j.jtherbio.2020.102716. Epub 2020 Sep 4. PMID: 33077129.

9. Zaramo TZ, Green JK, Janis JE. Practical Review of the Current Management of Frostbite Injuries. Plast Reconstr Surg Glob Open. 2022 Oct 24;10(10):e4618. doi: 10.1097/GOX.0000000000004618. PMID: 36299821; PMCID: PMC9592504.

10. Persitz J, Essa A, Ner EB, Assaraf E, Avisar E. Frostbite of The Extremities - Recognition, Evaluation and Treatment. Injury. 2022 Oct;53(10):3088-3093. doi: 10.1016/j.injury.2022.07.040. Epub 2022 Jul 26. PMID: 35914986.

11. Bruen KJ, Ballard JR, Morris SE, Cochran A, Edelman LS, Saffle JR. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. Arch Surg. 2007 Jun;142(6):546-51; discussion 551-3. doi: 10.1001/archsurg.142.6.546. PMID: 17576891.

12. Wagner C, Pannucci CJ. Thrombolytic therapy in the acute management of frostbite injuries. Air Med J. 2011 Jan-Feb;30(1):39-44. doi: 10.1016/j.amj.2010.08.006. PMID: 21211711; PMCID: PMC4496156.

13. Gross EA, Moore JC. Using thrombolytics in frostbite injury. J Emerg Trauma Shock. 2012 Jul;5(3):267-71. doi: 10.4103/0974-2700.99709. PMID: 22988410; PMCID: PMC3440898.

14. Gonzaga T, Jenabzadeh K, Anderson CP, Mohr WJ, Endorf FW, Ahrenholz DH. Use of Intra-arterial Thrombolytic Therapy for Acute Treatment of Frostbite in 62 Patients with Review of Thrombolytic Therapy in Frostbite. J Burn Care Res. 2016 Jul-Aug;37(4):e323-34. doi: 10.1097/BCR.0000000000000245. PMID: 25950290; PMCID: PMC4933583.

15. Hutchison RL, Miller HM, Michalke SK. The Use of tPA in the Treatment of Frostbite: A Systematic Review. Hand (N Y). 2019 Jan;14(1):13-18. doi: 10.1177/1558944718800731. Epub 2018 Sep 19. PMID: 30227720; PMCID: PMC6346356.

16. Melissa Mullen, Tracey Zachary, Richard Foley, Zubin Irani. Thrombolysis for Frostbite: A Case Study and Clinical Considerations, Journal of Radiology Nursing, Volume 38, Issue 4, 2019, Pages 237-240,

17. Paine RE, Turner EN, Kloda D, Falank C, Chung B, Carter DW. Protocoled thrombolytic therapy for frostbite improves phalangeal salvage rates. Burns Trauma. 2020 Apr 10;8:tkaa008. doi: 10.1093/burnst/tkaa008. PMID: 32341921; PMCID: PMC7175769.

18. Lee J, Higgins MCSS. What Interventional Radiologists Need to Know About Managing Severe Frostbite: A Meta-Analysis of Thrombolytic Therapy. AJR Am J Roentgenol. 2020 Apr;214(4):930-937. doi: 10.2214/AJR.19.21592. Epub 2020 Feb 5. PMID: 32023122.

19. Poole A, Gauthier J, MacLennan M. Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. CMAJ Open. 2021 May 21;9(2):E585-E591. doi: 10.9778/cmajo.20200214. PMID: 34021017; PMCID: PMC8177911.

20. Murphy J, Endorf FW, Winters MK, Rogers C, Walter E, Neumann N, Weber L, Lacey AM, Punjabi G, Nygaard RM. Bleeding Complications in Patients with Severe Frostbite Injury. J Burn Care Res. 2022 Dec 9:irac180. doi: 10.1093/jbcr/irac180. Epub ahead of print. PMID: 36482743.