American Burn Association Clinical Practice Guidelines on the Treatment of Severe Frostbite

Lucy Wibbenmeyer, MD, FACS[*], Alexandra M. Lacey, MD, RD, FACS[†], Frederick W. Endorf, MD[‡], Sarvesh Logsetty, MD, FRCS, FACS[‖], Anne L. L. Wagner, MD, FACS[$], Angela L. F. Gibson, MD, PhD[¶], and Rachel M. Nygaard, PhD[‡]

ABSTRACT

This Clinical Practice Guideline addresses severe frostbite treatment. We defined severe frostbite as atmospheric cooling that results in a perfusion deficit to the extremities. We limited our review to adults and excluded cold contact or rapid freeze injuries that resulted in isolated devitalized tissue. After developing population, intervention, comparator, outcomes (PICO) questions, a comprehensive literature search was conducted with the help of a professional medical librarian. Available literature was reviewed and systematically evaluated. Recommendations based on the available scientific evidence were formulated through consensus of a multidisciplinary committee. We conditionally recommend the use of rapid rewarming in a 38 to 42°C water bath and the use of thrombolytics for fewer amputations and/or a more distal level of amputation. We conditionally recommend the use of "early" administration of thrombolytics (≤12 hours from rewarming) compared to "later" administration of thrombolytics for fewer amputations and/or a more distal level of amputation. No recommendation could be formed on the use of vascular imaging studies to determine the use of and/or the time to initiate thrombolytic therapy. No recommendation could be formed on the use of intravenous thrombolytics compared to the use of intra-arterial thrombolytics on fewer amputations and/or a more distal level of amputation. No recommendation could be formed on the use of iloprost resulting in fewer amputations and/or more distal levels of amputation. No recommendation could be formed on the use of diagnostic imaging modalities for surgical planning on fewer amputations, a more distal level of amputation, or earlier timing of amputation.

In conjunction with *the American Burn Association (ABA) Clinical Practice Guideline (CPG)* ad hoc *Committee,* a multidisciplinary ABA team including clinicians with experience in frostbite management and frostbite researchers was selected to develop CPGs for the treatment of severe frostbite in adults (≥18 years of age) defined as atmospheric cooling resulting in a perfusion deficit to the extremities (hence referred to as severe frostbite). This committee includes all the listed authors for this CPG.

From the [*]Department of Surgery, University of Iowa, Iowa City, IA 52242, USA; [†]Department of Surgery, Regions Hospital, Saint Paul, MN 55101, USA; [‡]Department of Surgery, Hennepin Healthcare, Minneapolis, MN 55415, USA; [‖]Departments of Surgery, Psychiatry, and Children's Health, University of Manitoba, Winnipeg, Manitoba R3E 3P5, Canada; [$]Department of Surgery, Vanderbilt University Medical Center, Nashville, TN 37212, USA; [¶]Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA

AUTHOR CONTRIBUTIONS

L.W.: research—mediwound, avita, mallincrodt; consulting—allosource, mallincrodt, mediwound. A.M.L., F.W.E., S.L., and A.L.L.W.: none. A.L.F.G.: research/consulting—Mallinckrodt. R.M.N.: scientific consulting (editing/writing)—Eicos Scientific.

Address correspondence to Rachel Nygaard, PhD, Department of Surgery, Hennepin Healthcare, 701 Park Ave, P5, Minneapolis, MN 55415 USA. Email: rachel.nygaard@hcmed.org

https://doi.org/10.1093/jbcr/irad022

PURPOSE

The purpose of this CPG is to make recommendations, based on the available scientific literature, on the treatment of severe frostbite. Early medical advances in frostbite treatment include rapid rewarming, oral ibuprofen, topical aloe vera, pressure relief, and wound care.[1–3] A major advancement in the science of frostbite treatment occurred with the use of thrombolytics to reduce the injury caused by reperfusion following rewarming.[4] Most research on the treatment and management of frostbite injury are limited to single-center reports from high-volume centers.[5–11] However, many frostbite-injured patients present to smaller or more rural emergency departments (EDs) and not burn centers with expertise in managing severe frostbite injury. The philosophy that "time is tissue" in frostbite injury makes the rapid identification, initiation of therapy, and potential transfer to a higher level of care essential to reduce significant morbidity.[12–14] To address this deficiency, we sought to critically review the current literature and provide guidance related to each of our developed population, intervention, comparator, outcomes (PICO) questions.

These guidelines do not define the standard of care for acute severe frostbite diagnosis and management and should not be viewed as prescriptive in nature. These guidelines are based on a systematic review and evaluation of the quality of available evidence that address the specific PICO questions and are intended only to help guide clinicians who care for patients with acute severe frostbite. Bedside clinical judgment is always prioritized in the care of an individual patient with an acute frostbite injury.

USERS

This CPG will be of most use to emergency personnel, emergency, trauma, and burn nurses and physicians who provide care to severe frostbite patients in the ED, Burn Intensive Care Unit (ICU), surgical ICU, and during recovery. This CPG can also be a reference to patients as consumers of medical care.

CLINICAL PROBLEM AND SCIENTIFIC BACKGROUND

Frostbite injury and its sequelae affects both the military and civilian populations. The incidence of frostbite among both populations is increasing. In the 2020/2021 winter season, frostbite was the most common type of cold injury among active-duty military, resulting in a crude overall incidence of 35.4 per 100,000 person years; a greater than 25% increase over the prior season.[15] Civilians also incur frostbite injuries and the incidence in this population, like the military, also appears to be increasing. Nygaard et al. examined frostbite injury in the civilian population using the National Trauma Databank (NTDB) and the National Burn Repository (NBR) and showed an increase in the number of frostbite injuries reported from 2007–2014 to 2002–2011, respectively.[16] This was corroborated by the National Inpatient Sample of the Healthcare Cost and Utilization Project (HCUP), with the calculated incidence rate of frostbite injuries increasing from 0.66/100,000 in 2016 to 1.21/100,000 in 2018.[17] Over 3 years, this equated to over 8000 admissions for frostbite injury in the United States.[17]

Frostbite-injured patients are also a significant burden on hospital resources. Using the NBR, frostbite injury resulted in significantly higher cost and utilization of resources compared to similarly injured burn patients.[18] Moreover, using the 2016 and 2017 Nationwide Readmission Database of the HCUP, the unplanned readmission rate following frostbite injury is high (35.4%, 95% CI 32.2–38.6%).[19] The average total cost and length of stay (LOS) for unplanned readmissions is $236,872 and 34.7 days, respectively; which contributes to the cost of treating frostbite.[19]

Disability following frostbite injury is not well reported in the literature, with most studies focusing on the immediate hospital or perioperative period.[20] National studies report the rate of amputation in severe frostbite injury between 20% and 30%.[17,19,21] A single-center study reported the rate of surgical revision of the primary amputation was required in nearly a quarter of cases.[22] In addition to the amputation burden, Ervasti et al., in a case series 4 to 11 years after second-degree frostbite injury, found that 53% of patients had hypersensitivity to cold, 40% had numbness, and 13% were not able to work at the same level prior to injury.[23] In a study of U.S. military cold injury, 67% of patients reported persistent symptoms of neurovascular injury 6 months following frostbite injury and 8% had to be reassigned due to injury.[24] These studies support the need to assess long-term sequelae following frostbite injury and to consider these issues when treating frostbite.

The pathophysiology of frostbite involves ischemia, inflammation, and coagulation, lending itself to multiple possible medical interventions.[25–27] Frostbite-related tissue damage occurs in two phases. The initial phase includes the actual freezing injury, which begins with superficial tissue cooling, increased blood viscosity, and microvascular vasospasm as the body shunts warm blood to the core. As the tissues continue to cool, ice crystals form in the interstitial spaces and within the cells causing desiccation and direct physical damage. Blood is further shunted away from the injured tissue and thrombi form in the damaged microvasculature. The tissue ischemia elicits an inflammatory cascade in the damaged tissue. Upon rewarming of the injured extremity, a reperfusion injury occurs resulting in increasing edema, the release of multiple inflammatory and prothrombotic factors, and leukocyte infiltration. Diminishing the toxic triad of ischemia, inflammation, and coagulation of frostbite and restoring blood flow to prevent irreversible ischemia is the goal of treatment. Most treatment algorithms focus on rapid rewarming, thrombolytics (in appropriately screened patients) with continued anticoagulation, ibuprofen, wound care with aloe vera, and offloading pressure or weight to injured extremity.[2,5,26,28–30] Further treatment of the injured extremity is guided by diagnostic imaging or the traditional teaching of watchful waiting for clinical demarcation prior to definitive surgery. Ideally, successful treatment preserves limb length and soft tissue thereby decreasing sequela and reducing disability.

METHODS

For the development of this guideline, the CPG Committee met virtually on several occasions and communicated electronically. Through discussion and consensus, the committee identified clinically important questions and definitions pertaining to the topic of "treatment of severe frostbite injury." The questions were designed using a PICO approach (Patient: The patient population to whom the recommendations apply, Intervention: The therapeutic or diagnostic intervention of interest, Comparator: The alternative approach to the intervention [used in the control group], Outcome: The outcome(s) of interest for the clinical problem). The authors developed the following seven clinically important questions surrounding the topic of treatment of severe frostbite injury:

Among adults with severe limb frostbite, does rapid rewarming in a 38 to 42°C water bath, compared to not using rapid rewarming in a 38 to 42°C water bath, result in (a) fewer amputations and/or (b) a more distal level of amputation?

Among adults with severe limb frostbite does the use of vascular imaging studies (e.g. digital subtraction angiography [DSA], multiphase technetium-99m-methylenediphosphonate bone scintigraphy [bone scintigraphy], single-photon emission computed tomography fused with CT [SPECT/CT], microangiography with intravenous [IV] indocyanine green fluorescence [MA], and magnetic resonance angiography [MRA]), compared to not using these studies, affect (a) the use of thrombolytic therapy, and/or (b) the time to initiate thrombolytic therapy?

Among adults with severe limb frostbite, does the use of thrombolytic therapy, compared to not using thrombolytic therapy, result in (a) fewer amputations, and/or (b) a more distal level of amputation?

Among adults with severe limb frostbite, does the use of IV thrombolytics, compared to the use of intra-arterial (IA) thrombolytics, affect (a) the number of amputations and/or (b) the level of amputation?

Among adults with severe limb frostbite, does early administration of thrombolytics (≤12 hours from completion of rewarming), compared to later administration of thrombolytics (>12 hours from completion of rewarming but less than 24 hours), result in (a) fewer amputations and/or (b) a more distal level of amputation?

Among adult patients with severe limb frostbite, does the use of iloprost, compared to not using iloprost, result in (a) fewer amputations, and/or (b) a more distal levels of amputation?

Among adults with severe limb frostbite, does the use of diagnostic imaging modalities for surgical planning, including angiography, bone scintigraphy, microangiography, CT/A, SPECT, and MRI/MRA, compared to no imaging, affect the (a) number of amputations, (b) the level of amputation, and/or (c) the timing of amputation?

Search Strategy

A literature search for these seven PICO questions was conducted by a professional medical librarian. The search included the following databases: MEDLINE via Ovid, Embase via Elsevier, Cochrane Central Register of Controlled Trials (Central) via Wiley, and Cumulative Index of Nursing and Allied Health Literature (CINAHL) via EBSCO. For maximum comprehensiveness, the search was designed to retrieve all records that included the frostbite subject heading for all the databases or the keyword "frostbite" in the title, abstract, or author-supplied keywords fields for the first three databases and in any field in CINAHL. For MEDLINE, the most comprehensive segment (Ovid MEDLINE(R) ALL) was searched, which includes records with the following statuses: MEDLINE, Publisher, In-Data-Review, In-Process, and PubMed-not-MEDLINE records from NLM (national library of medicine). All databases were searched from inception to March 14, 2022, and no language or other limits were applied.

The search yielded a total of 5047 articles and after automatic deletion the final total was 3877 articles (Figure 1). Rayyan™ reference management software was used to upload and organize the articles (Rayyan Systems Inc., Cambridge, MA). Following manual removal of 752 duplicate articles, two committee members (R.N. and L.W.) independently evaluated the titles and abstracts of the remaining 3125 citations to identify articles suitable for full-text review. Further duplicates, preclinical articles, articles published only as abstracts, review articles, surveys, case reports, articles not available in English, and unrelated articles were excluded. Consensus between the two reviewers (R.N. and L.W.) was reached on April 15, 2022, and 35 articles were selected for initial full-text review.

Articles selected for initial full-text review were then independently screened for inclusion by three committee members (R.N., A.L., and L.W.) to determine if they addressed any of the PICO questions, based on the following mandatory set of inclusion criteria: 1) The study had to involve adults ≥18 years of age with severe limb frostbite from atmospheric cooling resulting in a perfusion deficit, 2) included patients were treated for frostbite injury using the therapeutic and/or diagnostic method of interest, 3) included a comparator (e.g. no thrombolytics or no imaging, etc.), and 4) at least one of the predefined PICO outcomes had to have been measured and reported. Following an independent review, the three reviewers (R.N., A.L., and L.W.) met virtually and reached consensus on which articles to finally include on May 26, 2022. Eight articles met these criteria and have been included in this CPG (Table 1 and Supplementary Table 1).

The eight included articles were systematically and independently evaluated by three committee members (R.N., A.L., and L.W.) using the critical appraisal form described by Law et al.[36] These members then met virtually on June 15, 2022 to compare each other's results and scores. Differences in total scores were resolved by consensus. The consensus scores for the quality of evidence in each of these studies are shown in Table 2. Sub-committees were then formed to address each PICO question and write a review using the selected articles, and where there was insufficient burn literature, randomized controlled trials and/or systematic reviews, experimental studies, and meta-analyses from the frostbite and non-frostbite literature were reviewed and included in the discussions of each question where appropriate. The committee met virtually on September 13, 2022, to form recommendations based on the available scientific evidence. The definitions for the final recommendations were based on majority vote of each contributing author.[37]

Question 1. *Among adults with severe limb frostbite, does rapid rewarming in a 38 to 42°C water bath, compared to not using rapid rewarming in a 38 to 42°C water bath, result in (a) fewer amputations and/or (b) a more distal level of amputation?*

For this question we defined rapid rewarming as using a warm water circulating or non-circulating bath set to 38 to 42°C for a duration of 15 to 30 minutes. We sought to identify the impact of rapid rewarming on the rate and level of amputation. We identified only one study, by Rogers et al. that addressed this specific question (Tables 1 and 2).[35]

Rogers et al. retrospectively reviewed a total of 208 patients with severe frostbite over a 7-year period, 131 of whom presented with frozen digits.[35] Using a previously published scoring system, the Hennepin Score,[38] bone scintigraphy scans were used to calculate the amount of tissue lacking perfusion on admission. Surgeons then used the same scoring system postoperatively to describe the actual tissue loss. A regression analysis was used to find predictors associated with limb salvage in these patients. The use of rapid rewarming was not a significant predictor of limb salvage (OR 2.75, $P = 0.119$). The authors concluded that rapid rewarming was not associated with limb salvage but cautioned that the study was underpowered to detect a statistical difference based on a post hoc analysis. A larger multicenter study of the practice was recommended.

Despite a paucity of data, rapid, early rewarming was one of the first treatment methods developed for severe frostbite injury and is widely used and recommended. Although

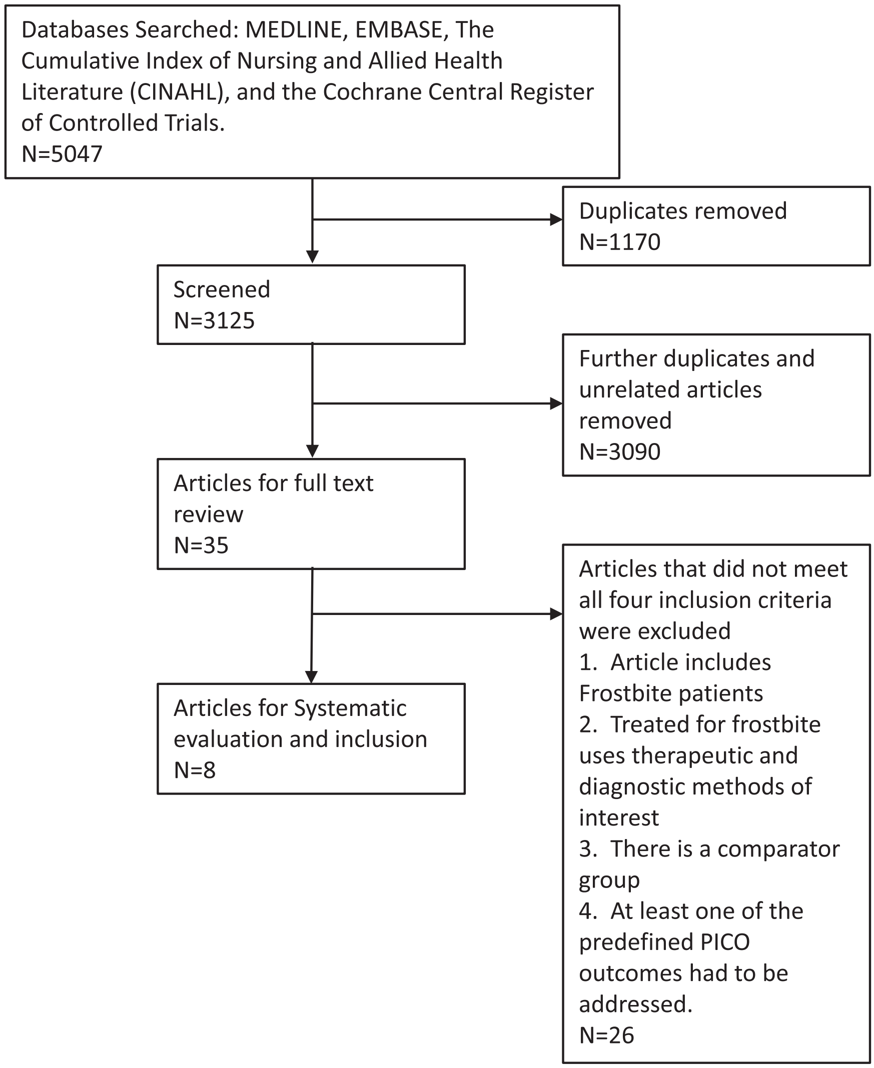

Figure 1. Consort diagram.

used in World War II, Mills et al. was the first to publish on the practices in 1960 on a largely civilian population.[3,39–41] Although his studies lacked scientific rigor, Mills et al. reported the largest cohort of patients undergoing the rapid rewarming.[3] While typically part of all frostbite management protocols, Rogers et al. found that only 66% of the patients admitted to outside centers with frozen limbs or digits underwent rapid rewarming in a water bath.[35] Similarly, in a Canadian study, 9 of 22 grade two through four frostbite patients underwent passive rewarming; however, none required amputation following treatment.[42]

Numerous preclinical studies demonstrated a significant reduction in tissue necrosis after rapid rewarming compared to allowing the limb to slowly return to normothermia.[43–52] However, most of these preclinical models utilize a freezing liquid bath to create the frostbite injury which is different from most frostbite injury observed in humans that is caused by slower atmospheric cooling. Additionally, as with many preclinical models, it is unclear if the basic pathophysiologic process of frostbite injury is the same as observed in humans. Further study and development of an atmospheric cooling model to assess pathophysiology and test new treatment modalities is needed.

Recommendations.

(a) Fewer amputations and/or (b) more distal level of amputation.

Conditionally recommend.

Rationale and Considerations.

There is compelling evidence for rapid rewarming in small animal studies, in which rapid rewarming was used in animals with extremities exposed to extreme cold temperatures.[43–52] Rapid rewarming showed an advantage with significantly less tissue loss compared with spontaneous rewarming.[43,52] These animal models were performed under highly controlled conditions and likely do not simulate all the variables seen in human frostbite. Based on this and unpublished usage in the military setting, the tenets of rapid rewarming were applied to human patients for the next 70 years.[3,35] Despite the intuitive benefits of rapid rewarming and its traditional use in frostbite, there are no well defined, large human studies

Table 1. Included manuscripts

Citation	Study Design	Sample Description	PICO-relevant outcomes	Other outcomes	Intervention and Comparator	Results
Al Yafi[31]	Retrospective case control	Admitted patients with frostbite between 2000–2006 (control) and 2012–2017 (IA tPA) $N = 18$	Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation? Q5. Does early administration of thrombolytics result in fewer or more distal amputation?	Angiographic findings (full, partial, or no response—number of patients) to total digits amputated (overall, not by patient). Detail factors associated with injury and inclusion/exclusion for tPA.	IA tPA ($N = 9$) no tPA ($N = 9$)	Q3: Overall amputation rate (by patient) IA tPA: 5 (56%) amputation no tPA: 6 (67%) $P = 0.6$ Digit amputation rate IA tPA: 41/108 (38%) No tPA: 29/78 (37%) Level of amputation: Amputations proximal to middle phalanges. IA tPA: 26/41 (63%) No tPA: 26/29 (90%) Q5: Time from injury to tPA: hours mean (SD) Amputation: 32 (15) Salvaged: 18.6 (7.5) $P = 0.15$ Time from admission to tPA: hours mean (SD) Amputation: 10.8 (12.3) Salvaged: 8.2 (7.4) $P = 0.72$
Bruen[32]	Retrospective with historical controls	Patients admitted 1995–2006 $N = 32$	Q2. Does vascular imaging affect the use or timing of tPA? Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation?	Primary objective was to evaluate the role for tPA to improve limb salvage Detail factors associated with injury and treatment algorithm.	Digital angiography ($N = 9$) vs no imaging ($N = 17$) IA tPA ($N = 6$) vs none ($N = 26$)	Q2: 2 with angio had no deficit and were not given tPA. 1 pt had tPA >24 h included in control group. Average time from admit to imaging: 4.5 h from admission (unclear if this includes pts with angio, but no tPA) Average time to tPA from exposure: 11.2 (±7.5) h Q3: Amputation Digits amputated/total digits involved No tPA: 97/234 (41%) tPA: 6/59 (10%) $P < 0.05$ Proximal amputation (extremity) No tPA: 14/57 (25%) tPA: 0/13

Table 1. Continued

Carmichael[15]	Retrospective	All frostbite admissions between November 30, 2015 and June 1, 2020	Q2: Does vascular imaging affect the use or timing of tPA? Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation? Q5. Does early administration of thrombolytics result in fewer or more distal amputation?	Primary objective to determine if initiation of tPA at referring centers (thereby foregoing formal vascular imaging) improved limb salvage. Detail factors associated with injury, remote treatment algorithm with inclusion/exclusion criteria, and salvage reported using a modified Hennepin Frostbite Score.	Tc99 bone scans vs no imaging (N = unclear for either group) IV tPA pre-transfer (N = 40) IV tPA after admission (N = 32) and no tPA (N = 127)	Q2: Unclear. No details of the use or timing of imaging. Q3: Any amputation Pre-transfer tPA $N = 9$ (22.5%) After admission tPA $N = 14$ (43.8%) No tPA $N = 76$ (56.8%) $P < 0.001$ Major amputation* Pre-transfer tPA $N = 4$ (10%) After admission tPA $N = 8$ (25%) No tPA $N = 27$ (21.3%) $P = 0.21$ *defined as Hennepin amputation score >5 Q5: Pre-transfer tPA resulted in lower risk of amputation OR 0.19 (0.05, 0.065) $P = 0.02$.
Cauchy[13]	Prospective randomized controlled trial Published as letter to the editor	Severe frostbite patient admitted between 1996 and 2008. Severe frostbite defined as having one digit with stage 3 or 4 frostbite	Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation? Q5. Does early administration of thrombolytics result in fewer or more distal amputation? Q6. Does iloprost therapy result in fewer or more distal amputations?	All had bone scans on day 2 and 8. Day 8 was used to predict likelihood of amputation. Reported severity of injury measured by visual assessment. Confirmation of predicted outcomes included as a Supplementary Table 1	Buflomedil (control $N = 15$, 106 digits) iloprost ($N = 16$, 142 digits) iloprost + tPA ($N = 16$, 159 digits)	Q3: Reduced amputation in both intervention group compared to control. Digits amputated Control: 47/407 (11.5%) Iloprost + rt-PA: 5/159 (3.1%) $P < 0.03$ Q5: Digits amputated Treated ≤12 h Control: 13/271 (4.8%) Iloprost + rt-PA: 0/79 (0%) Treated >12 h Control: 34/136 (25%) Iloprost + rt-PA: 3/15 (20%) Q6: Digits amputated Control: 47/407 (11.5%) Iloprost: 0/142 (0%) Iloprost + rt-PA: 5/159 (3.1%) $P < 0.01$ and $P < 0.03$

Table 1. Continued

Heard[33]	Retrospective and nested case control	Frostbite patients admitted January 2010–April 2018. $N = 102$ 12 tPA	Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation?	Report factors associated with need for any surgical intervention, detail factors associated with injury, and anatomic location(s) of injury.	No tPA ($N = 90$) IA ($N = 9$) or IV tPA ($N = 3$) Nested case control: tPA $N = 12$ No tPA $N = 28$	Q3: Amputation: tPA 2 (16.7%) no tPA: 10 (35.7%) $P = 0.285$.
Nygaard[12]	Retrospective	Severe frostbite patients (with documented perfusion deficit on Tc99 bone scan) admitted between 2006 and 2014 ($N = 73$)	Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation? Q5. Does early administration of thrombolytics result in fewer or more distal amputation?	Detail factors associated with injury, time to treatment, and salvage reported using Hennepin Frostbite Score.	IV tPA ($N = 45$) no tPA ($N = 28$)	Q3: Amputation (by patient) tPA: 16/45 (36%) No tPa: 16/28 (57%) $P = 0.092$ Salvage rate tPA: 74% no tPA: 55% $P = 0.061$. Q5: 26.8% decreased salvage with each hour delay of tPA ($P = 0.006$)
Patel[34]	Retrospective	all admitted patients with frostbite from 2000 to 2017.	Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation? Q5. Does early administration of thrombolytics result in fewer or more distal amputation?		IA tPA ($N = 8$) no tPA ($N = 9$)	Q3: Those receiving tPA had less digits at risk amputated and decreased LOS. Digits amputated IA tPA: 12/80 (15%) No tPA: 77/100 (77%) Q5: Amputation based on time to tPA <12 h: $N = 3$ with 12 digits amputated <24 h: $N = 3$ with 0 digits amputated <48 h: $N = 2$ with 0 digits amputated

Table 1. Continued

Rogers[35]	Retrospective	2014–2020 admitted with severe frostbite $N = 208$ Admissions with frozen limbs/digits $N = 131$ (direct $N = 68$ and transfer $N = 63$).	Q1. Does rapid rewarming result in fewer or more distal amputation? Q3. Does the use of thrombolytic therapy result in fewer or more distal amputation?	Rate of utilization of rapid rewarming and other rewarming techniques by admission type (direct admit vs transfer) Multivariable regression analysis to assess factors associated with limb/digit salvage (measured by the Hennepin Frostbite Score)	All admissions: Rapid rewarming $N = 103$ vs none or other warming $N = 105$. Subgroup presenting with frozen limbs/digits (cohort for regression analysis): Rapid rewarming $N = 96$. Direct admit $N = 55$ (91.2%) Transfer $N = 41$ (65.1%)	Q1: Rapid rewarming aOR 4.76 (0.67, 33.88) $P = 0.119$ Q3: tPA aOR 11.9 (1.57, 89.4) $P = 0.016$

Table 2. Assessment of included manuscripts based on Law et al.[36]

			Sample		Outcomes		Intervention			Results					
Citation	Study Purpose	Literature Review	De-tail	Jus-tified	Reli-able	Valid	Detailed Description	Contam-ination	Co-Intervention	Statistical Analysis	Analysis Appropriate	Clinical Importance	Dropouts Reported	Conclusions Appropriate	Total Score*
Al Yafi[31]	1	1	0	1	1	0	1	1	0	1	1	1	0	0	9
Bruen[32]	1	1	0	1	0	1	1	0	0	1	1	1	1	0	9
Carmi-chael[15]	1	1	0	1	1	0	1	0	0	1	1	1	1	1	10
Cauchy[13]	1	0	0	0	1	1	0	0	0	1	1	1	0	0	6
Heard[33]	1	1	0	1	1	1	1	1	0	1	1	1	1	1	12
Nygaard[12]	1	1	1	1	1	1	1	1	0	1	1	1	0	1	12
Patel[34]	1	1	0	1	0	0	1	0	0	1	1	1	0	0	7
Rogers[35]	1	1	0	1	1	1	1	1	0	1	1	1	0	1	11

*Total score possible is 14.
Additional details are available in Supplementary Table 1.

addressing its effect on limb salvage in patients with severe frostbite. However, given the evidence combined with expert opinion, the practice is likely not harmful and provides benefit over slow or room temperature rewarming. Caution should be used to ensure rewarming temperatures are not excessive causing additional thermal injury and the limbs are not at risk of re-freezing.[6,53] Additionally, consideration should be given to not prolong the resulting warm ischemia time prior to evaluation and definitive treatment at a burn or tertiary care center.[5,6]

Question 2. *Among adults with severe limb frostbite does the use of vascular imaging studies (e.g. DSA, bone scintigraphy, SPECT/CT, microangiography, and MRA), compared to not using these studies, affect (a) the use of thrombolytic therapy, and/or (b) the time to initiate thrombolytic therapy?*

For this question we explored the use of vascular imaging studies in severe limb frostbite. Our comparator was no use of vascular imaging studies. We sought to determine the impact of imaging on use and timing of thrombolytic therapy. We identified two low quality retrospective studies that met inclusion criteria (Tables 1 and 2).[14,32]

The first study was a retrospective chart review by Bruen et al. in which they included 21 patients from 2001 to 2006.[32] Their primary objective was to evaluate the role for tPA to improve limb salvage and as such the results are reported according to use of tPA and not the presence or absence of imaging. The imaging used to assess salvage rate was digital angiography. Nine of the 21 patients presented within 24 hours; all were noted to have a perfusion deficit on bedside Doppler examination and were within the predefined treatment window to receive digital angiography. Seven (77.8%) had abnormal studies and went on to receive tPA. One of these patients was greater than 24 hours after exposure and was then included in the control group. There were an additional 11 control patients from 1995 to 2000 with severe frostbite that were also reviewed that did not include imaging or thrombolytics resulting in a total control group of 26 patients. Using digital imaging reduced the number of patients who would have qualified for thrombolytics by clinical examination by 22%. Identification of those who would benefit from thrombolytics through use of imaging as a diagnostic tool to assess perfusion is reported in numerous publications. Of note, the authors report that they were able to obtain imaging on average 4.5 hours from admission and on average 11.2 hours from the end of exposure. Overall, this study had a small sample size and included a very heterogeneous collection of individuals which were compared to a mix of historic and contemporary controls.

The second included study was a retrospective study by Carmichael and included 199 patients over 5 years from 2015 to 2020.[14] This study evaluated if initiation of tPA, prior to formal imaging, at the referring hospital, improved limb salvage following severe frostbite injury as compared to after imaging at the tertiary center. This study included outcomes in patients treated with tPA at the referring hospital (40 patients), treated with tPA at their tertiary center (22 patients after transfer and 10 direct admission patients), or not treated with tPA (127 patients). It did not directly address the question of the effect of imaging on the use or timing of tPA therapy. There are numerous sources of potential bias including their own admission that they were not able to accurately track time from rewarming to tPA administration. The authors indicate that formal perfusion assessments were not conducted at referring centers and, even at their tertiary center, they felt that imaging quality was initially too low in resolution to estimate injury severity during the study period. It is unclear as to who received imaging at the referring sites or how many received imaging prior to tPA at the tertiary center, but they conducted bone scans on all patients after tPA administration. Limb salvage was based on a modified Hennepin score[38] calculated after warming and based on either pre-tPA photographs, pre-tPA physical exam, or post-tPA bone scintigraphy scans and compared to the final amputation level; however, neither this process nor the breakdown of patients were described in detail. Overall, those who received prehospital tPA, prior to imaging, were more likely to have no amputation or more distal amputations as compared to the other two groups. The authors concluded that the increased salvage rates in the early initiation group was secondary to decreased ischemia time, but this data is not reported in the paper and remains speculative.

The practice of using formal imaging became part of standard protocols after the landmark paper by Twomey et al.[4] Theirs was the first study to utilize thrombolytic therapy to reduce morbidity following severe frostbite injury. As part of their protocol, patients who presented with severe frostbite underwent bone scintigraphy scans to assess perfusion deficit following rewarming (16 historic controls and 19 study patients). This method allowed them to determine which patients had tissue at risk and to quantify the limb salvage. However, outcomes were based on historic controls and included insufficient detail to determine effectiveness of thrombolytic treatment on severe frostbite.

Recommendations.

(a) the use of thrombolytic therapy.

No recommendation. Currently there is insufficient scientific evidence to answer the question of the use of vascular imaging studies to determine the use of thrombolytic therapy.

Rationale and Considerations.

As thrombolytic therapy is expensive, reserving its use to indicated patients would be a potential advantage. Studies report a range of 4.3% to 33% of frostbite patients that were diagnosed with severe frostbite injury lacked a perfusion deficit when assessed by formal imaging.[30,32,54] The risk from imaging, beyond the reaction to the dye, is the potential for a false positive perfusion defect to be identified, subjecting the patient to thrombolytics, and the consequent potential complications.[55] This is counterbalanced to the risk of false negative imaging in which a potentially salvageable limb/digit is not treated with thrombolytics and is subsequently amputated. Cauchy et al. described a visual assessment to assess likelihood of predicted amputation, but this has not been widely adopted in the United States and warrants further study. Given the low risk of complications reported with thrombolytic therapy and the successful limb salvage rate reported in single-center studies, imaging prior to thrombolytics may not be beneficial especially if it extends the warm ischemia time.[11,12,14,29,33,55]

(b) The time to initiate thrombolytic therapy.

No Recommendation. At the present time there is insufficient evidence to determine whether vascular imaging affects the timing of thrombolytic therapy.

Rationale and Considerations.
The only study to report time from admission to imaging time was Bruen et al. with an average of 4.5 hours.[32] Some publications have reported time from admission or rewarming to thrombolytic therapy and the study by Lacey et al. detail their efforts to reduce warm ischemia time in severe frostbite injury.[12–14,29,56] While not directly assessing the impact of imaging on time to tPA, they report using bedside MA and/or clinical exam alone when assessing post-rewarming perfusion deficit to reduce time to tPA.[56] Additionally, the study by Carmicheal et al. showed improved results, without increasing adverse sequelae, by administering tPA prior to transfer and forgoing imaging, but no details were provided regarding warm ischemia or time to treatment.[14] Overall, any potential delay posed by vascular imaging is largely dependent upon the resources at each individual institution and therefore should be considered by the attending physician within the larger picture of the patient's injury timeline, injury severity, and options for treatment.

Question 3. *Among adults with severe limb frostbite, does the use of thrombolytic therapy compared to not using thrombolytic therapy, result in (a) fewer amputations, and/or (b) a more distal level of amputation?*

For this question, we reviewed the use of thrombolytics to treat severe limb frostbite. We included both IA and IV methods of delivering thrombolytic therapy as current practices include both methods of treatment. We were able to identify eight studies on the impact of thrombolytic therapy on amputation rates (Tables 1 and 2). Seven of eight studies were retrospective single-center studies with one prospective, randomized, non-peer reviewed clinical trial.[12–14,31–35]

Cauchy et al. found that iloprost in addition to IV tPA (N = 16) resulted in 19% of patients requiring amputations compared to 60% of the control group (N = 15; $P < 0.03$).[13] This data, while the only prospective randomized study, is only available in a Letter to the Editor and a full peer reviewed study was never published. Other papers supporting the use of thrombolytic therapy include Bruen et al. and Patel et al.[32,34] Bruen examined the use of IA tPA vs a mixed cohort of historic and contemporary controls discussed in detail in PICO question 2. They found a significant decrease in the number of amputations with IA tPA (6 of 59 digits at risk vs 97 of 234 digits, $P < 0.05$). They also found that there were less proximal amputations (transmetatarsal amputations or higher) in the intervention group versus control (0 vs 14).[32] Patel et al. found that IA tPA resulted in significantly less amputations in eight treated patients compared to nine controls (12/80 at risk digits vs 77/100 digits, $P = 0.003$).[34] Similarly, Rogers et al. reported significant improvement in tissue salvage, when controlling for other factors, with the use of IV tPA in a retrospective review of prospectively collected data of 131 patients (aOR 11.9 [CI 1.57, 89.4] $P = 0.016$).[35]

Alternatively, Nygaard et al. in a retrospective review of prospectively collected data in patients found that time to tPA was important but in the same paper found that patients who received IV thrombolytics had a similar rate of amputation to those who did not (50% in 45 patients vs 36% in 28 patients, P = 0.092).[12] Although the salvage rate in this limited sample size increased the risk of a type 2 error, results trended towards significance ($P = 0.06$). As mentioned above, a larger study performed in a non-overlapping population by the Hennepin group did find a significant difference in those treated with and without tPA.[35] Carmichael et al. reported a higher risk of amputation in the group receiving no tPA as compared to both groups receiving tPA (59.8% vs 31.9%, $P < 0.001$).[14] They compared amputations in patients treated with IV tPA prior to transfer to their institution, treated with IV tPA at their institution, and patients not treated with tPA (the latter two groups included both transfer and direct admit patients). They found that patients treated with IV tPA prior to transfer had fewer amputations than either the group of patients who did not receive IV tPA or patients treated with IV tPA at their hospital.[14] However, they also found that the group who received IV tPA at their hospital after transfer had no significant differences in odds of amputation as the group who did not receive tPA. This raises questions about the severity of frostbite injury in patients treated prior to transfer and the time of warm ischemia in the transferred patients.[14] There is no quantification of the amount of tissue at risk or tissue salvaged described in this paper as pre-tPA imaging was either not obtained or suboptimal. Additionally, they did not assess differences in level of amputation. Al Yafi et al. was unable to find a difference in outcomes (digital or per patient amputation rate) treated with thrombolytics (N = 9) vs the controls (N = 9).[31] However, they do report more proximal amputations in the group not treated with tPA (amputation proximal to middle phalange: 90% vs 63%).[31] The intervention group had a very long warm ischemia time which may have confounded these results. Heard et al. found no significant difference in need for amputation in their matched case-control study using both IV and IA tPA; however, the sample size of treated patients was only nine.[33] These single-center studies are small, heterogenous, and lack pertinent details including variations in how the salvage rates were calculated, important covariates, and in study design.

Extrapolating from animal research, Twomey et al. reported the first use of thrombolytics for clinical frostbite in their sentinel paper ushering in a new era of frostbite treatment.[4,50] This study led to numerous subsequent observational studies reporting on thrombolytics; most lacking comparator groups and details regarding confounders.[4,30,38,42,54,57–61] However, these studies show a greater than 70% salvage success rate with low complications.[5,10,11,25,62]

One limitation in the use of thrombolytics is the concern for bleeding complications. The rate of bleeding complications following thrombolytic therapy in severe frostbite injury is largely undescribed or limited to small case series.[12,33,42,54] Reported complications typically include bleeding from catheter sites, femoral pseudoaneurysm, retroperitoneal hematoma, or bleeding from other traumatic wounds. In the only study reporting complications following treatment of >100 patients with tPA, Murphy et al. found bleeding complications requiring a change of management or an intervention (i.e. blood transfusion) in 8.4% (12 of 143) of patients within 24 hours of treatment with IV tPA.[55] A recent review by Drinane et al. reported complication rates of 2.7% and 3.7% for IV and IA tPA therapy, respectively.[11]

Recommendation.

(a) Fewer amputations and (b) a more distal level of amputations.

We conditionally recommend that thrombolytics be initiated in appropriately screened severe frostbite patients to both decrease the need for amputation and reduce the level of amputation needed.

Rationale and Considerations.

Overall, the one prospective study and the seven retrospective studies demonstrate a trend towards improved salvage with thrombolytic therapy both in terms of fewer amputations and a more distal level of amputations—depending on the scoring system or outcome measure used. The exact extent of reduced amputation and improved salvage is unknown at this time and warrants a large, multicenter clinical trial. Studies report relatively low rates of complications following use of tPA which include extremity hematomas, retroperitoneal hematomas, or other minor bleeding.[33,42,54,55] Overall, the data would support the use of thrombolytic therapy (either IV or IA) for the treatment of severe frostbite though the exact extent of improved salvage cannot be quantified based on currently available literature.

Question 4. *Among adults with severe limb frostbite does the use of IV thrombolytics compared to the use of IA thrombolytics affect (a) the number of amputations and/or (b) the level of amputation?*

No studies fit the inclusion criteria comparing the two routes of tPA of administration.

Thrombolytic treatment focuses on reducing the injury caused by reperfusion following rewarming. For frostbite injury thrombolytics have been given both IA and IV. Twomey et al. began treating selected frostbite patients with IA thrombolytics (tPA) in 1989.[4] Upon observing perfusion improvements in untreated limbs that suggested systemic circulation of thrombolytics in those receiving only IA delivery, they began testing varying doses of IV thrombolytics.[4] All of the study patients had abnormal perfusion by bone scintigraphy scan and underwent tPA. The amputation rate was 19% in the study group with only three patients with no response. Heard et al. also reported on a limited number of patients treated with either IA (N = 9) or IV (N = 3) tPA at their center.[33] Neither study, however, compared outcomes between the treatment types. The overall reported salvage rate for the 17 reviewed studies is over 70% irrespective of the route of thrombolytics.[11,25]

Recommendations.

(a) Number of amputations and/or (b) level of amputation.

No recommendation. There are no studies which directly answer the question of whether IA or IV thrombolytics should be used to reduce the number of amputations or improve the level of amputation.

Rationale and Considerations.

It is apparent that thrombolytics are a key tool in the treatment of severe frostbite. Determination if IA or IV thrombolytic therapy is superior could not be clarified based on the current literature available. Further head-to-head comparison studies are needed to determine whether one route of administration is superior; however, the reduced resource burden and ability to treat multiple limbs simultaneously using IV tPA will likely preclude a randomized trial. Other considerations to be investigated include safety of each route of delivery in patients who may be undergoing a mental health crisis or substance use withdrawal and cost of therapy.

Question 5. *Among adults with severe limb frostbite, does "early" administration of thrombolytics (≤12 hours from completion of rewarming) compared to "later" administration of thrombolytics (>12 hours from completion of rewarming but less than 24 hours) result in (a) fewer amputations and/or (b) a more distal level of amputation?*

For this question we defined time to thrombolytics as the time from documented or estimated initiation of rewarming to the initiation of thrombolytic therapy. This includes both rapid rewarming and passive rewarming in most studies. We did not specify which thrombolytic drug was used, which route of thrombolytic administration, or which adjunctive therapies could be used. The comparator group was thrombolytic administration >12 hours from rewarming. The time from rewarming to thrombolytic therapy is discussed as warm ischemia time.

Five studies met inclusion criteria for review (Tables 1 and 2).[12–14,31,34] Four were retrospective analysis at single sites and one was a randomized clinical trial. There was variability in the exact measure of warm ischemia time by each center and one specifically noted they could not measure it accurately.[14] Although warm ischemia time is defined as the time from rewarming to treatment as this is sometimes unknown, some studies report time from admission to treatment.

Cauchy et al. conducted a randomized clinical trial that included three treatment groups: buflomedil (N = 15), iloprost (N = 16), and iloprost plus tPA (N = 16). The digit amputation rate in patients treated with iloprost plus tPA within 12 hours was 2 of 144 (1.4%) and 3 of 15 (20%) in those treated after 12 hours.[13] There are no details related to the breakdown of severity of injury between the two groups. Additionally, this study was published as a letter to the editor and has not been peer reviewed. Nygaard et al. showed a decrease in tissue salvage based on the time from rewarming to the initiation of thrombolytic therapy.[12] This did not specifically divide the groups into early and late as defined in this question (12 hour time mark). A regression analysis showed that each hour of warm ischemia time resulted in a decrease in salvage of 28.1% (P = 0.011).[12] Carmichael et al. published their experience initiating tPA at referring centers in order to reduce warm ischemia time in transfer patients. They showed that patients who had pre-transfer thrombolytics had lower odds of amputation (OR 0.19 95% CI 0.05–0.65, P = 0.01).[14] While they postulate this was due to reduced warm ischemia time, they were not able to specifically track time to thrombolytics.

Al Yafi et al. retrospectively reviewed 18 patients (9 with tPA and 9 controls).[31] They were unable to detect a significant difference in amputation rates in those treated with or without thrombolytics. They reported a non-significant trend towards longer time from injury to tPA (32 vs 18.6 hours) and admission to tPA (10.8 vs 8.2 hours) in patients that required amputation compared to those that did not.[31] Patel et al. found that IA tPA (N = 8) resulted in significantly less amputations compared to control (12/80 at risk digits vs 77/100 digits, P = 0.003).[34] They reported the time to treatment for each patient and the number of digits amputated, but did not provide the number of digits at risk in this table. Three patients were treated within 12 hours and had 12 digits with amputations. No amputations occurred in patients treated within 24 hours (N = 3) or within 48 hours (N = 2). The authors state that their study is underpowered to provide a specific recommendation on the temporal relationship between exposure time and outcome.[34]

Recommendations.

(a) Fewer amputations and/or (b) more distal level of amputations.

Conditional recommendation. There is low level scientific evidence showing initiation of thrombolytics earlier after rewarming decreases the number and level of amputation. Overall, there is a trend in the data to support that a shorter warm ischemia time is better for tissue salvage and lower amputation rates both in terms of fewer total amputations and more distal level of amputations depending on the scoring system used. However, based on the extent and quality of the data, we cannot recommend a specific time window for the initiation of thrombolytics.

Rationale and Considerations.

Outcomes vary widely based on the amount of warm ischemia time. The Hennepin group observed a 26.8% decrease in salvage with each hour delay in delivery of thrombolytics.[12] The importance of warm ischemia time is echoed by Cauchy et al., who showed improvement in salvage if thrombolytics were delivered less than 12 hours from rewarming.[13] More recently, the Colorado group reported on their experience initiating thrombolytics at outside centers based on clinical exam alone.[14] They found a significant risk reduction in amputation in transfer patients who began tPA at the outside center.[14] Upon review of the existing literature, the warm ischemia time was either not obvious or variable, ranging from <24 hours to >48 hours from the time of rewarming to thrombolytics delivery. Regardless, many centers opt for an optimal range for treatment of between 12 and 24 hours which is well supported by the work of Mills et al. in Alaska and the Hennepin group.[3,4] However, this should be considered in the broader picture of the patient's clinical picture and not used as a means to exclude patients from potentially limb saving treatment.

Question 6. *Among adult patients with severe limb frostbite does the use of intravenous (IV) iloprost, compared to not using iloprost, result in (a) fewer amputations, and/or (b) a more distal level of amputation?*

For this question we explored the use of IV iloprost in severe frostbite. Our comparator was no use of iloprost. Iloprost is currently not available in the United States but is used in Canada and Europe. We identified only one study that met the inclusion criteria (Tables 1 and 2).[13]

The study by Cauchy et al. was published as a letter to the editor in the New England Journal of Medicine.[13] The authors reviewed the use of iloprost in a randomized, open label study enrolling 47 frostbitten patients (grades 2–4). Iloprost, given as a 6-day infusion was compared to a group receiving IV buflomedil and a group receiving iloprost and IV tPA. All groups received rapid rewarming and aspirin. The reported outcome was predicted amputation based on perfusion deficit on day 8 bone scintigraphy—a method described in a prior study.[63] Overall the predicted amputation rate was 11.5% with zero amputations in the iloprost only group, 3.1% in the iloprost with tPA group, and 39.6% in the control group.[13] Despite being the only study meeting our criteria, there were several weaknesses. First it was published in letter form and therefore did not undergo peer review. Second, although the study was randomized, the iloprost + tPA group had over eight times more severe frostbite and the randomization process was not clarified. Finally, digit salvage was presented in only a binary fashion and was not compared to the pretreatment severity of injury. Lack of this pretreatment assessment obscured the second outcome of digit/limb preservation.

Although the above study by Cauchy et al. was the only study meeting our criteria, one cohort study and several case studies report on the experience with iloprost in Canada and Europe. In the largest published cohort study, Poole et al. included 22 patients presenting <72 hours with grades 2–4 frostbite.[42] All patients received IV iloprost and those presenting with grade 4 also received IV tPA (Alteplase). There were no amputations in those with grade 2 or 3 frostbite.[42] The overall salvage rate was 79.6% falling to 50% for the seven patients with grade 4 (over two thirds of the amputated digits occurring in one patient).[42]

Recommendations.

(a) Fewer amputations and/or (b) more distal level of amputations.

No recommendation.

Rationale and Considerations.

The evidence from the one included study and other smaller cohort and case studies demonstrate some promise,[13,42,64,65] however additional larger studies are required. Additionally, these studies need to include a U.S. frostbite population which is markedly different than the largely mountaineering injuries reported in these studies. Any benefit of using iloprost with thrombolytics cannot be determined based on the current literature available and a trial assessing these outcomes is warranted. Iloprost can be given in a delayed fashion which may provide a therapy for those outside of the treatment windows for thrombolytics, however this also requires further study.

Question 7. *Among adults with severe limb frostbite, does the use of diagnostic imaging modalities for surgical planning, including angiography, bone scintigraphy, microangiography, CT/A, SPECT, and MRI/MRA compared to no imaging, affect the (a) number of amputations, (b) the level of amputation, and/or (c) the timing of amputation?*

This question sought to determine the efficacy of imaging in guiding surgical intervention. The comparator group was no imaging. Surgical intervention for frostbite debridement and amputation is often delayed months after the injury to let the tissue demarcate. Delaying surgery, however, can lead to longer hospital stays, increased risk of infection, longer pain management strategies, and added cost for our healthcare systems and patients. No articles fulfilled our inclusion criteria. However, a few single-center studies have successfully used imaging to guide definitive surgery or predict amputation levels.

Numerous small case series report successful used of imaging for surgical planning.[66–69] In a larger study including 88 patients, Cauchy et al. evaluated the use of bone scintigraphy performed at 2 and 8 days following severe frostbite injury.[63] Scans included 53 hands, 48 feet, and 13 involving both feet and hands. They reported a high sensitivity (0.65), specificity (0.99), and positive predictive value (0.92) for absence of radiotracer uptake in the bone phase correlating with eventual amputation level.[63] The predictive value increased when a second scan was performed at day 8 as poorly perfused areas on the first scan progressed on the second scan.[63] This finding, combined with prior reports discussing outcomes with delayed use of imaging in surgical planning, prompted the authors to recommend rescanning if poorly perfused areas were detected on the first scan. The timing and the details of the definitive surgical operations were not provided in the paper.[63]

In a retrospective/prospective study Lacey et al. evaluated the utility of MA with IV indocyanine green fluorescence compared to bone scintigraphy in defining amputation level.[56] The authors compared amputation level to imaging in three groups of patients (N = 130): patients that had bone scintigraphy (82 patients), patients that had bone scintigraphy and a MA (26 patients, following treatment with IV thrombolytics and within 12 hours of each other) and patients that had MA alone (22 patients).[56] They found that bone scintigraphy was strongly correlated with final amputation, while MA showed a slightly stronger positive correlation with amputation level. MA can be performed rapidly, at the bedside, is low cost, and avoids ionizing radiation; however, the downside of this modality (as with the other modalities discussed) is that it requires specialized technicians/training and equipment and does not assess bone viability. The study did not address the impact of imaging on the number of amputations, the level of amputation, or the timing of amputations.

To overcome the limitations of bone scintigraphy's ability to assess anatomic detail, others have investigated the use of SPECT/CT. This modality fuses bone scintigraphy with CT images creating superior anatomic detail that can be used to demarcate viable tissue. In a retrospective review, Kraft evaluated use of SPECT/CT in 7 patients and 19 extremities.[70] In all seven patients the level of amputation matched the prediction of viability on the imaging and no patient needed revision surgery.[70] Time to imaging was 12 days (4–27 days) and time to surgery was 17.7 days (5–30 days).[70]

Recommendations.

(a) Number of amputations: No recommendation.

Rationale and Considerations.
Although we cannot make a recommendation secondary to lack of evidence, it seems likely that bone scintigraphy or SPECT/CT may provide accurate guidance for watchful waiting and/or amputation level, respectively. The studies discussed show excellent prediction of amputation level and presumably of viable tissue, although the literature does not enable us to conclude that use of imaging modalities leads to fewer amputations.

(b) Level of amputation: No recommendation.

Rationale and Considerations.
The limited studies in the literature show imaging correlates with eventual amputation level.[56,63] A study comparing the surgeons proposed amputation level with preoperative imaging and actual amputation level would definitively answer this question.

(c) Timing of amputation: No recommendation.

Rationale and Considerations.
The literature is limited and further study is needed to definitively answer the question of timing of surgical intervention and the use of imaging compared to the current practice of watchful waiting.

IMPLEMENTATION AND NEXT STEPS

Overall, no strong guidelines can be recommended based on the current literature. We only found evidence to support conditionally recommending the use of rapid rewarming, thrombolytics (IV or IA), and early use of thrombolytics. This is similar to the findings of other recent reviews and management guidelines.[5,6] Emphasis should be given to early referral and transportation of severe frostbite patients to high-volume burn centers in order to screen for eligibility for thrombolytics and expedite definitive treatment.

The barriers to treatment include knowledge gaps, delays in patients seeking care, rapid identification of severity of injury, timely referral of severe frostbite patients to tertiary centers, and contraindications to thrombolytics therapy. To address knowledge gaps we recommend including up to date frostbite treatment in both established courses as the American Burn Association's Advanced Burn Life Support Class and American College of Surgeons Committee on Trauma Advanced Trauma Life Support Class as well as other outreach efforts to improve education at centers treating smaller numbers of frostbite injury. Contraindications to thrombolytics include pregnancy, significant concurrent trauma, recent surgery or hemorrhage within 10 days, or intracranial bleeding within 3 months.[5,29,33,54,55] Relative contraindications include moderate concurrent trauma, multiple freeze-thaw cycles, and prolonged warm ischemia time. Thrombolytics have a low adverse sequelae rate that should be considered in the setting of saving a limb or digit (see discussion in PICO question 3).

Future Research

There are several areas in need of consideration of future research aims. One is a standardized data collection process to include demographics, comorbidities, social determinants of health, and injury details such as warm ischemia time, diagnostic tests, measure of injury severity, intervention timing, adjuvant therapy, and outcomes. This data collection must include a standard methodology for measuring outcomes associated with frostbite injury. Researchers have reported amputation rates based on a per person, per digit, per bone segment, or an overall salvage rate. We would recommend a minimum report including per person amputation and an overall salvage rate. The specific details of per digit amputation are helpful, but only beneficial if we have a measure of the severity of injury as well as the actual level of the amputation. Severity of injury should be obtained by imaging or beside perfusion test after rewarming. Reporting of the timing of rewarming, time to post-rewarming testing, and post-rewarming treatment would improve accuracy as well. Additionally, delayed imaging may be used as an alternative outcome measure to definitive surgical intervention when assessing early treatment modalities. This would reduce bias associated with loss to follow-up or complications due to additional frostbite injury or infection.

Several questions could not be answered due to absence of evidence or low-quality evidence with no clear benefit with an absence of harm. Additionally, the impact of overlapping or additional supportive treatments remain unanswered. Examples of this include the intersection of the use of rapid rewarming and thrombolytics. The following would be areas for future scientific investigation:

Development of a suitable preclinical atmospheric freezing model of severe frostbite injury that mimics pathophysiology observed in human frostbite injury.
A well conducted comparison between adjuvant therapies and adjuvants plus thrombolytics.
Large study assessing the effect of varying warm ischemia times on thrombolytic effectiveness.
Comparison of the efficacy and safety of IA vs IV thrombolytics.
Evaluate the impact of supportive therapies including topicals and long-term anticoagulation.
Assess outcomes associated with IV iloprost in a U.S. frostbite population.
Compare outcomes using IV iloprost plus thrombolytics against thrombolytics alone.
Assess the efficacy of delayed imaging to guide earlier surgical therapy.
Assess long-term outcomes in the patients treated and not treated with thrombolytics.

In order to address the above research priorities, implementation of a standard frostbite dataset for registries could significantly improve our research and outcome measures. This could be best achieved through the ABA. These variables should include:

Measure of severity of frostbite injury after rewarming and documentation of method measure.
Documentation of use or non-use of rapid rewarming in water bath.
Description of any use of thrombolytics and method of delivery.
Recorded time from rewarming to thrombolytics.
Recorded time from admission to thrombolytics.
Documentation of use of any continued anticoagulation and the length of time it was used.
Time to surgical management on primary admission or subsequent admissions.
Standard measure of severity of injury and level of amputation.

Quality Measures

In order to continue to advance the field of frostbite treatment, centers treating frostbite should assess their outcomes based on quality metrics. These metrics reinforce the philosophy that time is tissue in preserving ischemic limbs and could include:

Time to treatment (rewarming/thrombolytics assessment).
Use of rapid rewarming in a water bath (when presenting with frozen limbs or digits).
Assessment/workup for thrombolytic therapy.

Factors for further consideration include assessment of needs and social determinants of health in this population. Close collaboration with social workers and physical and occupational therapists can improve outcomes in this high-risk population.

SUPPLEMENTARY DATA

Supplementary data is available at *Journal of Burn Care & Research* online.

ACKNOWLEDGMENTS

The authors would like to thank: Drs. Irma Flemming, Bill Mohr, and John Twomey for their insight and discussion about frostbite management; Heather Healy for her medical library search expertise; and Dr. Robert Cartotto for his guidance through the process and developing this manuscript.

REFERENCES

1. Heggers JP, Robson MC, Manavalen K et al. Experimental and clinical observations on frostbite. Ann Emerg Med 1987;16:1056–62. doi:10.1016/S0196-0644(87)80758-8.
2. McCauley RL, Hing DN, Robson MC, Heggers JP. Frostbite injuries: a rational approach based on the pathophysiology. J Trauma 1983;23:143–7.
3. Mills WF. A discussion of the problem and a review of an Alaskan experience. Alaska Med 1973;15:27–47.
4. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. J Trauma 2005;59:1350–5. doi:10.1097/01.ta.0000195517.50778.2e.
5. Hickey S, Whitson A, Jones L et al. Guidelines for thrombolytic therapy for frostbite. J Burn Care Res 2020;41:176–83. doi:10.1093/jbcr/irz148.
6. McIntosh SE, Freer L, Grissom CK et al. Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. Wilderness Environ Med 2019;30:S19–32. doi:10.1016/j.wem.2019.05.002.
7. Handford C, Buxton P, Russell K et al. Frostbite: a practical approach to hospital management. Extrem Physiol Med 2014;3:7. doi:10.1186/2046-7648-3-7.
8. Handford C, Thomas O, Imray CHE. Frostbite. Emerg Med Clin North Am 2017;35:281–99. doi:10.1016/j.emc.2016.12.006.
9. Shenaq DS, Gottlieb LJ. Cold injuries. Hand Clin 2017;33:257–67. doi:10.1016/j.hcl.2016.12.003.
10. Hutchison RL, Miller HM, Michalke SK. The use of tPA in the treatment of frostbite: a systematic review. Hand (New York, NY). 2019;14:13–8. doi:10.1177/1558944718800731.
11. Drinane J, Kotamarti VS, O'Connor C et al. Thrombolytic salvage of threatened frostbitten extremities and digits: a systematic review. J Burn Care Res 2019;40:541–9. doi:10.1093/jbcr/irz097.

12. Nygaard RM, Lacey AM, Lemere A et al. Time matters in severe frostbite: assessment of limb/digit salvage on the individual patient level. J Burn Care Res 2017;38:53–9. doi:10.1097/BCR.0000000000000426.
13. Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. N Engl J Med 2011;364:189–90. doi:10.1056/NEJMc1000538.
14. Carmichael H, Michel S, Smith TM, Duffy PS, Wiktor AJ, Lambert Wagner A. Remote delivery of thrombolytics prior to transfer to a regional burn center for tissue salvage in frostbite: a single-center experience of 199 patients. J Burn Care Res 2022;43:54–60. doi:10.1093/jbcr/irab041.
15. Update: cold weather injuries, active and reserve components, U.S. Armed Forces, July 2016-June 2021. MSMR. 2021;28:2–10.
16. Nygaard RM, Endorf FW. Frostbite in the United States: an examination of the national burn repository and national trauma data bank. J Burn Care Res 2018;39:780–5. doi:10.1093/jbcr/irx048.
17. Endorf FW, Nygaard RM. Social determinants of poor outcomes following frostbite injury: a study of the national inpatient sample. J Burn Care Res 2021;42:1261–5. doi:10.1093/jbcr/irab115.
18. Nygaard RM, Endorf FW. Frostbite vs burns: increased cost of care and use of hospital resources. J Burn Care Res 2018;39:676–9. doi:10.1093/jbcr/iry033.
19. Endorf FW, Nygaard RM. High cost and resource utilization of frostbite readmissions in the United States. J Burn Care Res 2021;42:857–64. doi:10.1093/jbcr/irab076.
20. Regli IB, Strapazzon G, Falla M, Oberhammer R, Brugger H. Long-term sequelae of frostbite—a scoping review. IJERPH 2021;18:9655. doi:10.3390/ijerph18189655.
21. Endorf FW, Nygaard RM. Socioeconomic and comorbid factors associated with frostbite injury in the United States. J Burn Care Res 2022;43(3):646–51. doi:10.1093/jbcr/irab162.
22. Coward A, Endorf FW, Nygaard RM. Revision surgery following severe frostbite injury compared to similar hand and foot burns. J Burn Care Res 2022;43:1015–8. doi:10.1093/jbcr/irac082.
23. Ervasti O, Hassi J, Rintamäki H et al. Sequelae of moderate finger frostbite as assessed by subjective sensations, clinical signs, and thermophysiological responses. Int J Circumpolar Health 2000;59:137–45.
24. Taylor MS, Kulungowski MA, Hamelink JK. Frostbite injuries during winter maneuvers: a long-term disability. Mil Med 1989;154:411–2. doi:10.1093/milmed/154.8.411.
25. Lee J, Higgins MCSS. What interventional radiologists need to know about managing severe frostbite: a meta-analysis of thrombolytic therapy. Am J Roentgenol 2020;214:930–7. doi:10.2214/AJR.19.21592.
26. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. Hand Clin 2009;25:481–96. doi:10.1016/j.hcl.2009.06.004.
27. Imray C, Grieve A, Dhillon S; Caudwell Xtreme Everest Research Group. Cold damage to the extremities: frostbite and non-freezing cold injuries. Postgrad Med J 2009;85:481–8. doi:10.1136/pgmj.2008.068635.
28. Mills WJ, Whaley R, Fish W. Frostbite: experience with rapid rewarming and ultrasonic therapy. Part II. 1960 Alaska Med 1993;35:10–8.
29. Lacey AM, Rogers C, Endorf FW et al. An institutional protocol for the treatment of severe frostbite injury—a 6-year retrospective analysis. J Burn Care Res 2021;42:817–20. doi:10.1093/jbcr/irab008.
30. Lindford A, Valtonen J, Hult M et al. The evolution of the Helsinki frostbite management protocol. Burns 2017;43:1455–63. doi:10.1016/j.burns.2017.04.016.
31. Al Yafi MN, Danino MA, Izadpanah A, Coeugniet E. Using intra-arterial tPA for severe frostbite cases. An observational comparative retrospective study. J Burn Care Res 2019;40:907–12. doi:10.1093/jbcr/irz118.
32. 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;142:546–51; discussion 551. doi:10.1001/archsurg.142.6.546.
33. Heard J, Shamrock A, Galet C, Pape KO, Laroia S, Wibbenmeyer L. Thrombolytic use in management of frostbite injuries: eight year retrospective review at a single institution. J Burn Care Res 2020;41(3):722–26. doi:10.1093/jbcr/iraa028.
34. Patel N, Srinivasa DR, Srinivasa RN et al. Intra-arterial thrombolysis for extremity frostbite decreases digital amputation rates and hospital length of stay. Cardiovasc Intervent Radiol 2017;40:1824–31. doi:10.1007/s00270-017-1729-7.
35. Rogers C, Lacey AM, Endorf FW et al. The effects of rapid rewarming on tissue salvage in severe frostbite injury. J Burn Care Res 2021:irab218. doi:10.1093/jbcr/irab218.
36. Law M, Stewart D, Pollock N, Letts L, Bosch J, Westmorland M. Guidelines for critical review form - quantitative studies. Published online 1998. Available from https://canchild.ca/system/tenon/assets/attachments/000/000/366/original/quantguide.pdf accessed 22 Dec. 2022.
37. HPAC Workgroup Members. Update to the centers for disease control and prevention and the healthcare infection control practices advisory committee recommendation categorization scheme for infection control and prevention guideline recommendations; 2019. Available from https://www.cdc.gov/hicpac/workgroup/recommendation-scheme-update.html accessed 1 Dec. 2022.
38. Nygaard RM, Whitley AB, Fey RM, Wagner AL. The hennepin score: quantification of frostbite management efficacy. J Burn Care Res 2016;37:e317–22. doi:10.1097/BCR.0000000000000277.
39. Mills WJ, Frostbite WR. Experience with rapid rewarming and ultrasonic therapy - part 1. Alaska Med 1960;35:6–9.
40. Mills WJ, Whaley R, Frostbite FW. Experience with rapid rewarming and ultrasonic therapy - part 2. Alaska Med 1960;35:10–8.
41. Mills WJ, Whaley R, Frostbite FW. Experience with rapid rewarming and ultrasonic therapy - part 3. Alaska Med 1960;35:19–27.
42. Poole A, Gauthier J, MacLennan M. Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. CMAJ Open. 2021;9:E585–91. doi:10.9778/cmajo.20200214.
43. Pichotka J, Lewis RB. Effect of rapid and prolonged rewarming on local cold injury. U S Armed Forces Med J. 1951;2:1293–310.
44. Sullivan BJ, Leblanc MF. Effect of inositol and rapid rewarming on extent of tissue damage due to cold injury. Am J Physiol 1957;189:501–3. doi:10.1152/ajplegacy.1957.189.3.501.
45. Dawson D, Hardenbergh E. Effect of rapid rewarming on tissue survival of frozen rabbits' feet. J Appl Physiol 1958;12:155–63. doi:10.1152/jappl.1958.12.2.155.
46. Entin MA, Schultz GA, Baxter H. Effect of slow and rapid warming on prolonged chilling and freezing of the legs of dogs. Angiology 1954;5:486–99. doi:10.1177/000331975400500605.
47. Salimi Z, Wolverson M, Herbold D, Vas W, Salimi A. Treatment of frostbite with i.v. streptokinase: an experimental study in rabbits. Am J Roentgenol 1987;149:773–6. doi:10.2214/ajr.149.4.773.
48. Salimi Z, Wolverson MK, Herbold DR, Vas WF. Experimental assessment of tissue damage using Tc-99m pyrophosphate. Work in progress. Radiology 1986;161:227–31. doi:10.1148/radiology.161.1.3020608.
49. Yeager RA, Campion TW, Kerr JC, Hobson RW, Lynch TG. Treatment of frostbite with intra-arterial prostaglandin E1. Am Surg 1983;49:665–7.
50. Zdeblick TA, Field GA, Shaffer JW. Treatment of experimental frostbite with urokinase. J Hand Surg Am 1988;13:948–53. doi:10.1016/0363-5023(88)90278-X.
51. Purkayastha SS, Bhaumik G, Chauhan SKS, Banerjee PK, Selvamurthy W. Immediate treatment of frostbite using rapid rewarming in tea decoction followed by combined therapy of pentoxifylline, aspirin & vitamin C. Indian J Med Res 2002;116:29–34.
52. Fuhrman FA, Crismon JM. Studies on gangrene following cold injury: treatment of cold injury by means of immediate rapid warming. J Clin Invest 1947;26(3):476–85.
53. Fuhrman FA, Fuhrman GJ. The treatment of experimental frostbite by rapid thawing; a review and new experimental data. Medicine (Baltim) 1957;36:465–87. doi:10.1097/00005792-195712000-00002.
54. 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;37:e323–34. doi:10.1097/BCR.0000000000000245.
55. Murphy J, Endorf FW, Winters MK et al. Bleeding complications in patients with severe frostbite injury. J Burn Care Res 2022:irac180. doi:10.1093/jbcr/irac180.
56. Lacey AM, Fey RM, Gayken JR et al. Microangiography: an alternative tool for assessing severe frostbite injury. J Burn Care Res 2019;40:566–9. doi:10.1093/jbcr/irz112.
57. Tavri S, Ganguli S, Bryan RG et al. Catheter-directed intraarterial thrombolysis as part of a multidisciplinary management protocol of frostbite injury. J Vasc Interv Radiol 2016;27:1228–35. doi:10.1016/j.jvir.2016.04.027.
58. Paine RE, Turner EN, Kloda D, Falank C, Chung B, Carter DW. Protocoled thrombolytic therapy for frostbite improves phalangeal salvage rates. Burns Trauma 2020;8:tkaa008. doi:10.1093/burnst/tkaa008.
59. Jones LM, Coffey RA, Natwa MP, Bailey JK. The use of intravenous tPA for the treatment of severe frostbite. Burns 2017;43:1088–96. doi:10.1016/j.burns.2017.01.013.
60. Wexler A, Zavala S. The use of thrombolytic therapy in the treatment of frostbite injury: J Burn Care Res 2017;38:e877–81. doi:10.1097/BCR.0000000000000512.
61. Johnson AR, Jensen HL, Peltier G, DelaCruz E. Efficacy of intravenous tissue plasminogen activator in frostbite patients and presentation of a treatment protocol for frostbite patients. Foot Ankle Spec 2011;4:344–8. doi:10.1177/1938640011422596.
62. Drinane J, Heiman AJ, Ricci JA, Patel A. Thrombolytic salvage of the frostbitten upper extremity: a systematic review. Hand (New York, NY). 2022;17(3):397–404. doi:10.1177/1558944720940065
63. Cauchy E, Chetaille E, Lefevre M, Kerelou E, Marsigny B. The role of bone scanning in severe frostbite of the extremities: a retrospective study of 88 cases. Eur J Nucl Med Mol Imaging 2000;27:497–502. doi:10.1007/s002590050534.

64. MacLennan M, Poole A, Gauthier J. Use of fluorescence to visualize response to iloprost treatment for frostbite. CMAJ 2021;193:E1219–E1219. doi:10.1503/cmaj.202258.
65. Magnan MA, Gayet-Ageron A, Louge P et al. Hyperbaric oxygen therapy with iloprost improves digit salvage in severe frostbite compared to iloprost alone. Medicina 2021;57:1284. doi:10.3390/medicina57111284.
66. Greenwald D, Cooper B, Gottlieb L. An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. Plast Reconstr Surg 1998;102:1069–74. doi:10.1097/00006534-199809040-00023.
67. Salimi Z, Vas W, Tang-Barton P, Eachempati RG, Morris L, Carron M. Assessment of tissue viability in frostbite by 99mTc pertechnetate scintigraphy. Am J Roentgenol 1984;142:415–9. doi:10.2214/ajr.142.2.415.
68. Mehta RC, Wilson MA. Frostbite injury: prediction of tissue viability with triple-phase bone scanning. Radiology 1989;170:511–4. doi:10.1148/radiology.170.2.2911677.
69. Shenaq DS, Beederman M, O'Connor A, Teele M, Robinson MR, Gottlieb LJ. Urban frostbite: strategies for limb salvage. J Burn Care Res 2019;40:613–9. doi:10.1093/jbcr/irz062.
70. Kraft C, Millet JD, Agarwal S et al. SPECT/CT in the evaluation of frostbite. J Burn Care Res 2017;38:e227–34. doi:10.1097/BCR.0000000000000359.