# WORKSHEET for Evidence-Based Review of Science for First Aid

**Worksheet author(s)**
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**Date Submitted for review:** August 22, 2009

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### Clinical question.

Does rewarming of a localized injury (frostbite) improve outcome?

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### Is this question addressing an intervention/therapy, prognosis or diagnosis?

Intervention

### State if this is a proposed new topic or revision of existing worksheet.

Revision of worksheet

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### Conflict of interest specific to this question.

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No.

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### Search strategy (including electronic databases searched).

- PubMed search using ‘frostbite’ (MeSH term) AND ‘rewarming’ (MeSH term): 29 hits  
- PubMed search using (rewarming[MeSH Terms]) OR (rewarming)) AND ((frostbite[MeSH Terms]) OR (frostbite)): 79 hits  
- All PubMed searches updated automatically weekly since 10/08  
- Search of related articles in PubMed: 131 hits (120 excluded/duplicates)  
- Cochrane library using search terms “frostbite” and “cold injury”: 0 hits

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Embase search for terms ‘rewarming’/exp OR 'rewarming' AND [english]/lim AND [priority journals]/lim) AND ('frostbite'/mj AND [english]/lim AND [abstracts]/lim): 33 hits (all excluded or duplicates)

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Review of AHA Master Endnote library: 8 hits (6 excluded/duplicates)  
Manual search for title term ‘frostbite’ in Wilderness and Environmental Medicine journal: 8 hits (all 8 excluded/duplicates)  
Manual search of references from eMedicine.com article on Frostbite (no new hits)  
Forward search of Google Scholar using terms ‘frostbite’ and ‘rewarming’: 12 hits (all excluded/duplicates)

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### State inclusion and exclusion criteria.

**Included:** human and animal studies, case series, review articles specific for frostbite, English or Spanish language

**Excluded:** Review articles of general cold injuries; not true frostbite (e.g., hypothermia, chilblains, pernio, frostnip, cryoinjury); other therapy or treatment is primary focus of study (e.g., thrombolytics, pentoxyfylline, ultrasound); duplicate citations.

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### Number of articles/sources meeting criteria for further review:

13 articles from the initial search potentially meet inclusion criteria. An extensive number of pure review articles from the original search were eliminated. Articles included in review include 7 animal studies and 6 case series.

3 additional articles included from expanded PubMed search.
# Summary of evidence

## Evidence Supporting Clinical Question

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<td>Malhotra 1978 (A)</td>
<td>Twomey 2005 (A)</td>
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<td>Purkayastha 1993(A)</td>
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<td>Entin 1952 (A)</td>
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### Level of evidence

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Outcomes – Please define outcomes for this question, place them after letters below and use letters to identify studies which evaluate this outcome

- **A** = extent of tissue loss or damage
- **C** = no outcome described
- **E** =
- **B** = microscopic/vascular reperfusion
- **D** =

*Italics = Animal studies*
### Evidence Neutral to Clinical question

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### Evidence Opposing Clinical Question

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The majority of research studies on rewarming of frostbite injury have been performed in animals. Animal models are not uniform in techniques for inducing localized cold injury, timing of rewarming following cold injury, rewarming temperature, or methods of determining tissue loss. Seven LOE 5 animal studies (Fuhrman 1947, Crismon 1947, Entin 1952, Malhotra 1978, Purkayastha 1993 and 2002, Martinez 2002) provide fair to good supportive evidence for improved outcome as measured by tissue loss or return of circulation following rapid rewarming as compared to gradual rewarming with ambient temperature. The ideal temperature for rapid rewarming has been the subject of several studies but rewarming techniques have been limited to use of a water bath. Fuhrman (1947, pp 477) and Crismon (1947, p. 470) each found a water bath temperature of 42°C to be superior to rewarming at room temperature in terms of tissue loss and return of microvascular circulation. Entin (1952, p. 513) found decreased tissue loss following frostbite if rewarming was initiated without delay with water bath temperatures between 35 and 45°C. Purkayastha (1973; p.31 and 2002) found less tissue loss with a water bath temperature of 37°C vs. room temperature. Malhotra (1978, p. 875) found that water bath temperatures of 45°C or higher produced greater tissue loss, while temperatures between 37 and 39°C improved outcome compared with temperatures of 35, 41 and 43°C. Martinez (2002, p.226) found reductions in amount of tissue necrosis following rewarming using a water bath temperature of 38°C compared to gradual (room temperature) rewarming.

Human studies are limited to case series dating back to the 1950s and using protocols derived from early animal studies with water bath temperatures between 37–42°C or higher, versus room/ambient temperature gradual rewarming. Numbers in case series that look specifically at rapid rewarming are small, since most patients present after thawing has begun. Unfortunately almost all published case series fail to describe outcomes associated with rewarming protocols. Mills (1993, Part III, from original 1960 Alaska Medicine article series) found in his case series that patients with frostbite who subsequently underwent thawing followed by refreezing had much more severe tissue loss than those who did not sustain repeated freeze-thaw cycles, and he recommended that if there is risk of refreezing, then rewarming should be delayed until the patient is evacuated. Water bath temperatures used by Mills ranged between 42–48°C. There are no controlled human trials comparing rates of rewarming or rewarming temperatures. Twomey (2005) found a decrease in amputation rates when patients with severe frostbite and no perfusion after rapid rewarming were treated with IV or IA TPA, but success was only in patients who had warm ischemia times of 6 hours or less, cold exposure for less than 24 hours, and no evidence of repeated freeze-thaw cycles (LOE 4).

Task Force members questioned whether if a water bath was necessary for rewarming of frostbite injury versus alternative dry heat (as from disposable chemical heat packs) since rewarming by a water bath may not be feasible in wilderness/outdoor environments. Mills (1993, Part III, p.21) noted in his case series from the late 1940s that when rapid rewarming was used on frostbite injuries, patients rewarmed via a water bath at 110–118°F had less tissue loss than those rewarmed with dry heat. Sources of dry heat in this case series included engine muffler exhaust and other sources that could produce cutaneous burns; patients treated with dry heat had “disastrous results.” Sands (2009) recently reviewed characteristics of multiple different brands of disposable chemical hand and foot warmers and found that the duration of heat produced varied between brands and the maximum temperature reached ranged from 69 to 74°C – sufficient to cause thermal burns when placed on unprotected, insensate frostbitten skin. In light of these 2 studies and animal studies showing improved outcome with rapid rewarming in water at body temperature, it is appropriate to recommend that if rewarming is attempted in the field, it should be accomplished using water bath immersion at a temperature approximating normal body temperature.

Acknowledgements:
Citation List


Summary – Case series of 7 patients with frostbite treated with an inpatient protocol that included rapid rewarming at 40°C as well as other interventions such as NSAIDs. Outcomes not described. LOE 4 neutral.


Summary – One of the earliest animal studies of frostbite in rabbit ears, using rapid rewarming in a 42°C water bath and with the animal acting as its own control. Circulatory effects and subsequent tissue loss both evaluated.


Summary – This was a study using rat hindlegs and dog hindlegs and forelegs, first in an effort to produce a consistent model for study of frostbite, and subsequently to measure the percentage of tissue loss following severe frostbite injury combined with hypothermia by using gradual (room temperature) rewarming and rapid rewarming in a water baths at various temperatures. The authors also looked at the effect of delayed rapid rewarming (i.e., room temperature rewarming for 1, 2 or 3 hours after freezing injury followed by rewarming in 42°C water bath). There was less tissue loss when rewarming was between 35 and 45°C and when there was no delay between cessation of exposure to freezing temperatures and beginning of rapid rewarming. LOE 5, good supportive evidence.


Summary - A case series of 1261 frostbite victims describing treatment protocols, which include rapid rewarming in a 36°C water bath. Outcomes not described, confounders not identified, LOE 4 (Poor).


Summary – Animal model of frostbite in rabbit ears, treated with rapid rewarming at 42°C versus gradual (room temperature) rewarming, with outcome measurements of tissue loss, time to onset of gangrene, and extent of induration and scarring several weeks after injury. No statistical analysis performed, but compared to control group, animals in rapid rewarming group all had lesser degrees of necrosis and subsequent fibrosis/scarring. LOE 5, Good supportive evidence.


Summary - Review article of animal rewarming studies with additional data from authors prior animal studies. Emphasizes rapid rewarming as superior to gradual rewarming for treatment of frostbite, and notes that tissue loss increases with increasing duration of the frozen state.


PMID: 666681

Summary – In this animal study the authors compared rapid rewarming at various temperatures versus at ambient (room) temperature, looking at degree of tissue loss for the outcome. Each animal served as its own control. Good supportive level of evidence (5).

Summary – Animal model of frostbite using rabbit paws comparing rapid rewarming at 38°C versus rewarming gradually at room temperature (22°C), using extent of phalangeal necrosis as outcome. Groups included one group receiving hemodilution in addition to rewarming, but this was accounted for by including a group that did not receive hemodilution. Metatarsal necrosis was significantly greater in the control group (no hemodilution/22°C) than in the rapid 38°C rewarming group. LOE 5 Good supportive study.


Summary – This is the first of a 3 part series by Mills and Whaley originally published in Alaska Medicine in 1960 and again published in 1993, that is essentially a case series of frostbite victims treated by the authors beginning in the mid-1950s. The first part describes frostbite pathophysiology and rewarming techniques used by the authors (water bath, varying temperatures from 42 – 48°C). No outcomes or dates are presented in this first part. LOE 4, neutral.


This is “Mills 1993 – II” in the evidence tables

Summary – Part two of three part series of articles presenting a case series of 51 frostbite patients treated in the 1950’s. Part II focuses on the outcome in terms of tissue loss/amputations, demographics and pre-existing risk factors. This series of articles is frequently cited in review articles advocating rapid rewarming, but this particular article details only 7 patients treated by rapid rewarming in a water bath, 6 treated by application of snow or ice water immersion, 37 treated by rewarming gradually at room temperature, and 1 through excessive dry heat. Of the various modalities, 6/7 patients treated by rapid rewarming had “Type B” injury (least severe tissue loss), while 15/37 of those treated with gradual/room temperature rewarming had more severe tissue loss (Types C and D) and 19/37 had milder Type B tissue loss. Rewarming on nearly all patients was carried out prior to hospital presentation. Small group numbers prevent any statistical analysis but suggests improved outcome with rapid rewarming vs. gradual rewarming. LOE 4, fair supportive.


This is “Mills 1993 – III” in the evidence tables

Summary - Essentially a discussion or summary of a case series of 51 frostbite cases, each treated with rewarming but using different methods to rewarm, including dry warm packs as warm water baths. Describes observations of improved outcome using water baths versus dry heat, and recommends rewarming after shelter or rescue has occurred. LOE 4, fair supportive.


Summary – This is a commentary on the case series of 51 frostbite cases described in the 3 part article original published in 1960 and again in 1993 in Alaska Medicine, with an updated case series number of 1026. Details of the additional cases (treatment and outcomes) are not provided. This article summarizes the findings of the case series and provides management recommendations that include thawing with rapid rewarming. The author emphasizes that prognosis is poor when thawing is delayed, by excessive heat, or if a freeze-thaw-freeze injury occurs. LOE 4, Fair supportive.

Summary – Review article on rewarming techniques/temperatures.


Summary – Animal study using rat frostbite model with 5 different treatment groups including rapid rewarming at 37°C, plus control group. LOE 5, good supportive evidence.


Summary - Animal model of frostbite in rats, with control group allowed to rewarm at room temperature and treatment groups rewarmed at 37 – 39°C in a tea decoction. Treatment groups also received a variety of other interventions including aspirin, pentoxifylline and topical silver sulfadiazine. Outcome was tissue necrosis as measured by hind paw volume. LOE 5, fair supportive study (confounding interventions).

Sands WA, Kimmel WL, Wurtz BR, Stone MH and McNeal JR: Comparison of Commercially Available Disposable Chemical Hand and Foot Warmers. Wilderness and Environmental Medicine, 20, 33-38 (2009). Abstract: Objective.—Small chemical hand and foot warmers are used by many winter sport athletes and other outdoor enthusiasts. The purpose of this study was to characterize the thermal behaviors of 14 commercially available hand and foot warmers.

Summary: This study shows the wide range of maximum temperatures produced by chemical hand warmers, with several brands reaching temperatures between 69 and 74°C. The high temperatures reached, combined with loss of sensation with acute frostbite, support a recommendation to avoid direct application for active rewarming of frostbitten tissue.


Summary: This is a case series of patients with severe frostbite and without perfusion following rapid rewarming who were treated with IV or IA TPA and heparin, with a reduction in the number of predicted digit amputations. Failure to respond to TPA/heparin was found in patients who sustained greater than 24 hours of cold exposure, had warm ischemia times >6 hours or evidence of multiple freeze-thaw cycles. LOE 4, good indirect evidence supporting rewarming if 1)refreezing can be avoided and 2)patient can be evacuated for advanced medical care within 6 hours of rewarming.


Summary – Animal study using isolated gracilis muscle in 11 rats, with observed reperfusion and return of microcirculation occurring within 5-10 minutes after rewarming. At 42°C. Purpose of study was to develop a model for frostbite injury using intravital microscopy to evaluate the effects of early frostbite injury. LOE 5, neutral evidence.