Frostbite Interventions

THOR Conference 2024

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Disclosure

- Eicos Sciences – scientific consulting/writing – ended
- Triton Systems – scientific consulting - ended

- Discussing off-label use of thrombolytics

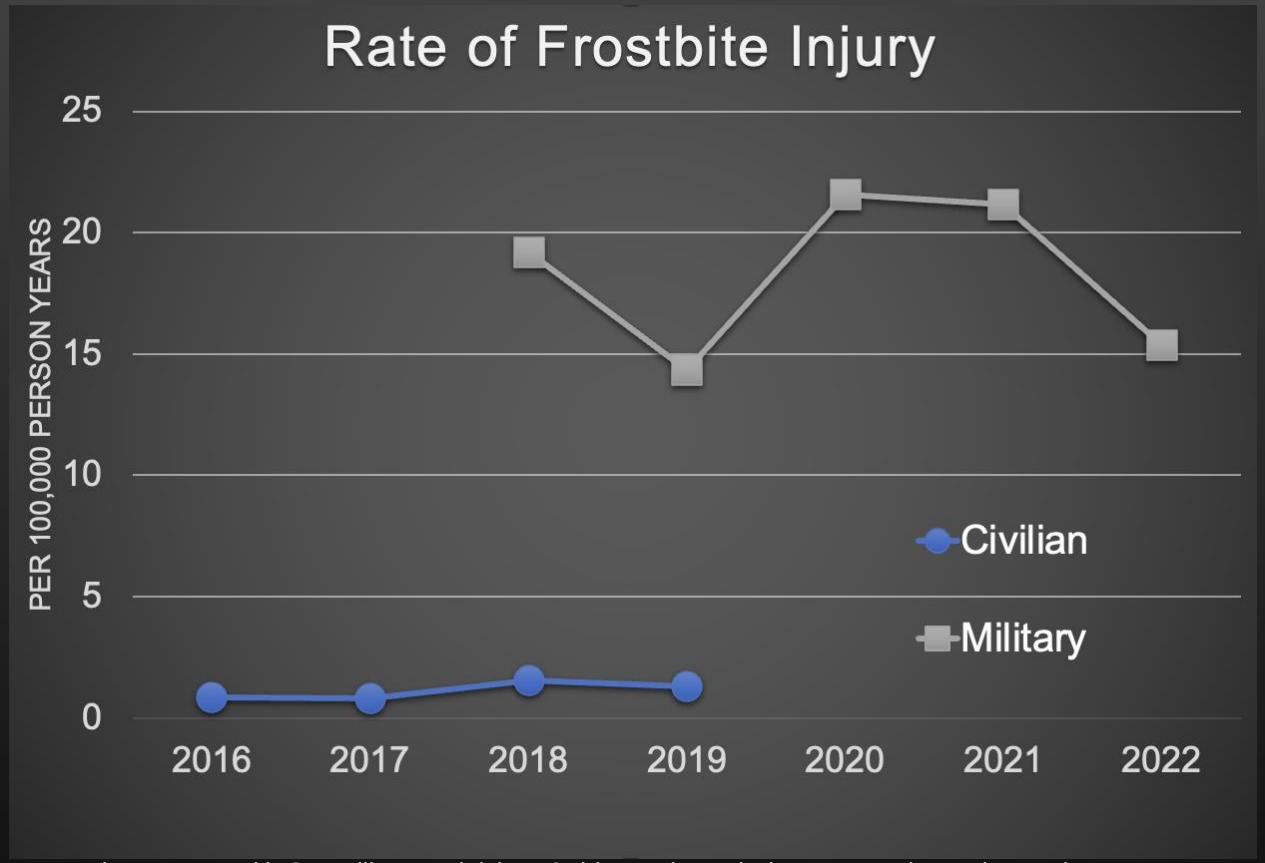
Objectives

- Understanding frostbite
- Interventions
- Going forward

Abbreviations & definitions

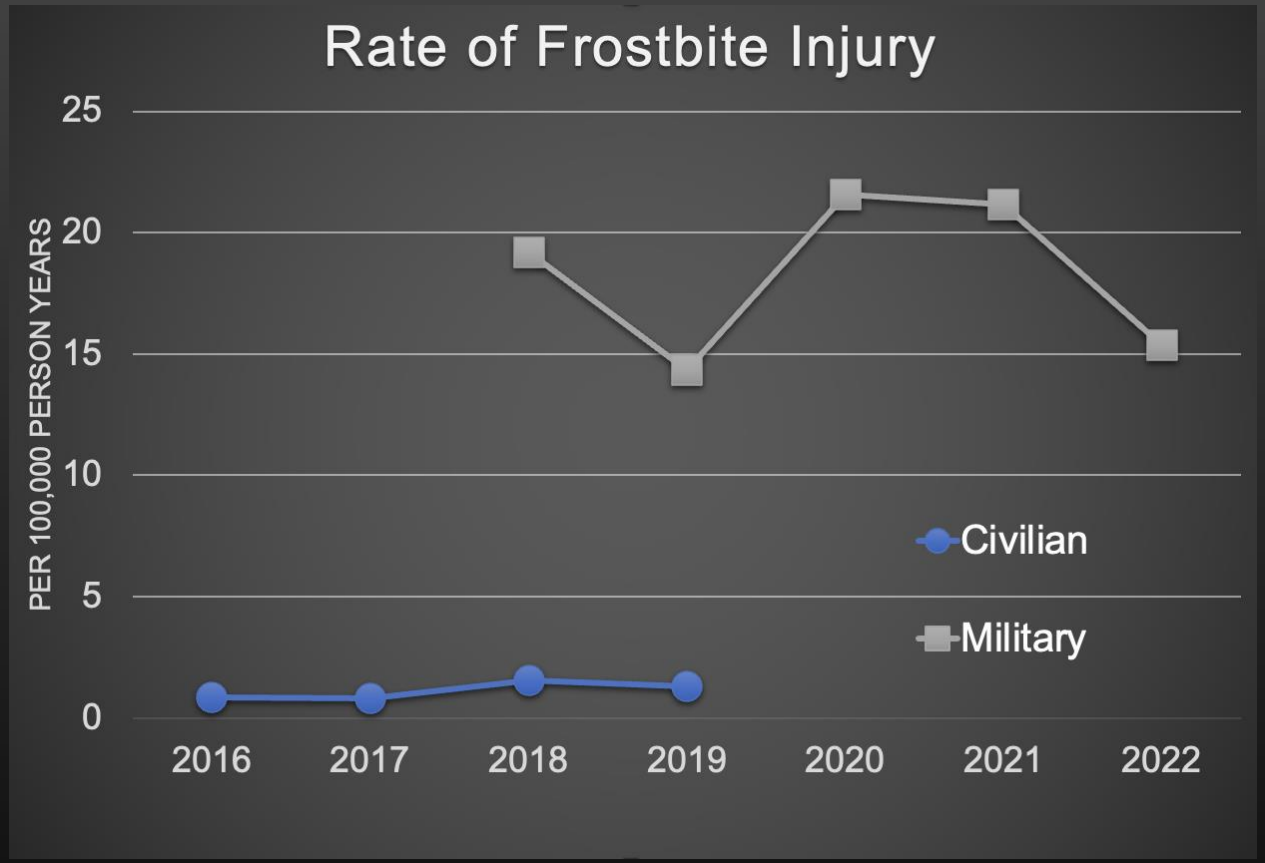
- tPA -> thrombolytics
- Rapid rewarming -> warming frozen extremity in (circulating) warm water (35-39C)

Frostbite impact on the military



- Armed Forces Health Surveillance Division. Cold Weather Injuries Among the Active and Reserve Components of the U.S. Armed Forces, July 2018-June 2023. MSMR. 2023 Nov 20;30(11):2-11. PMID: 38051632.
- Armed Forces Health Surveillance Division. Update: Cold Weather Injuries, Active and Reserve Components, U.S. Armed Forces, July 2015-June 2020. MSMR. 2020 Nov;27(11):15-24.
- Endorf FW, Nygaard RM. Social Determinants of Poor Outcomes Following Frostbite Injury: A Study of the National Inpatient Sample. J Burn Care Res. 2021 Nov 24;42(6):1261-1265.

Frostbite impact on the military



	US Armed Forces	HCMC	HCMC
18-19	257	551	71
19-20	195	317	85
20-21	296	514	41
21-22	287	928	62
22-23	202	759	96
Degree	1st - 4th	Encounters 1st - 4th	3rd - 4th

- Modified from: Armed Forces Health Surveillance Division. Cold Weather Injuries Among the Active and Reserve Components of the U.S. Armed Forces, July 2018-June 2023. MSMR. 2023 Nov 20;30(11):2-11. PMID: 38051632.
- Modified from: Endorf FW, Nygaard RM. Social Determinants of Poor Outcomes Following Frostbite Injury: A Study of the National Inpatient Sample. J Burn Care Res. 2021 Nov 24;42(6):1261-1265.

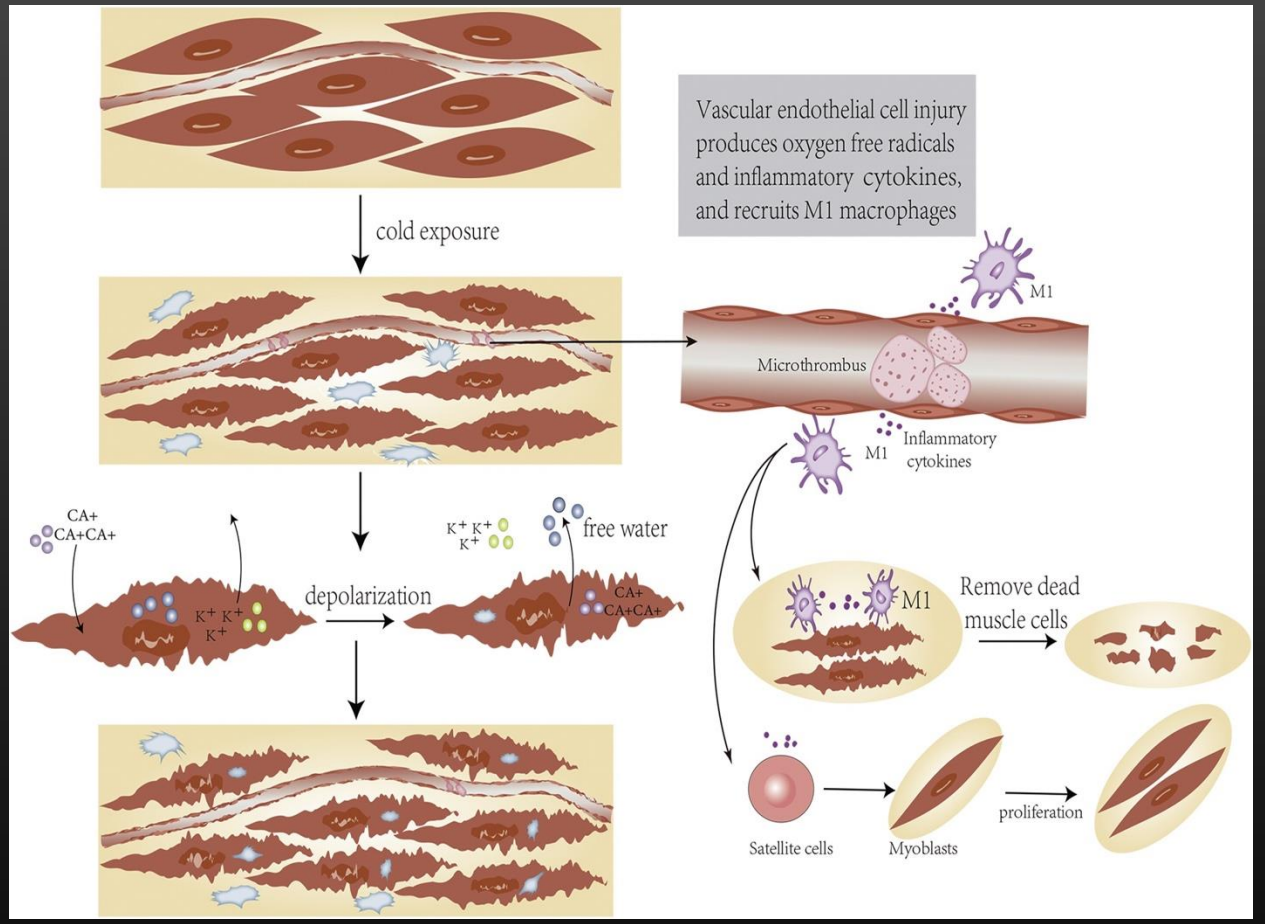
Frostbite impact on the military

Most soldiers (50-89%) could not fully return to duty or were discharged

Freezing Cold Injury (FCI/frostbite)

Pathophysiology of Severe Frostbite

- Initial Injury:
  - Ice crystal formation inside cells causes mechanical disruption and cell death.
- Vascular Changes:
  - Vasoconstriction reduces blood flow, causing ischemia and tissue necrosis.
- Rewarming Damage:
  - Reperfusion after rewarming leads to oxidative stress, inflammation, and edema.



Gao Y, Wang F, Zhou W, Pan S. Research progress in the pathogenic mechanisms and imaging of severe frostbite. Eur J Radiol. 2021 Apr;137:109605. doi: 10.1016/j.ejrad.2021.109605
Zafren, K. (2014). Frostbite: prevention and initial management. High Altitude Medicine & Biology, 15(2), 148-155.

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2023, VOL. 82, 2203923
https://doi.org/10.1080/22423982.2023.2203923

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The classification of freezing cold injuries - a NATO research task group position paper

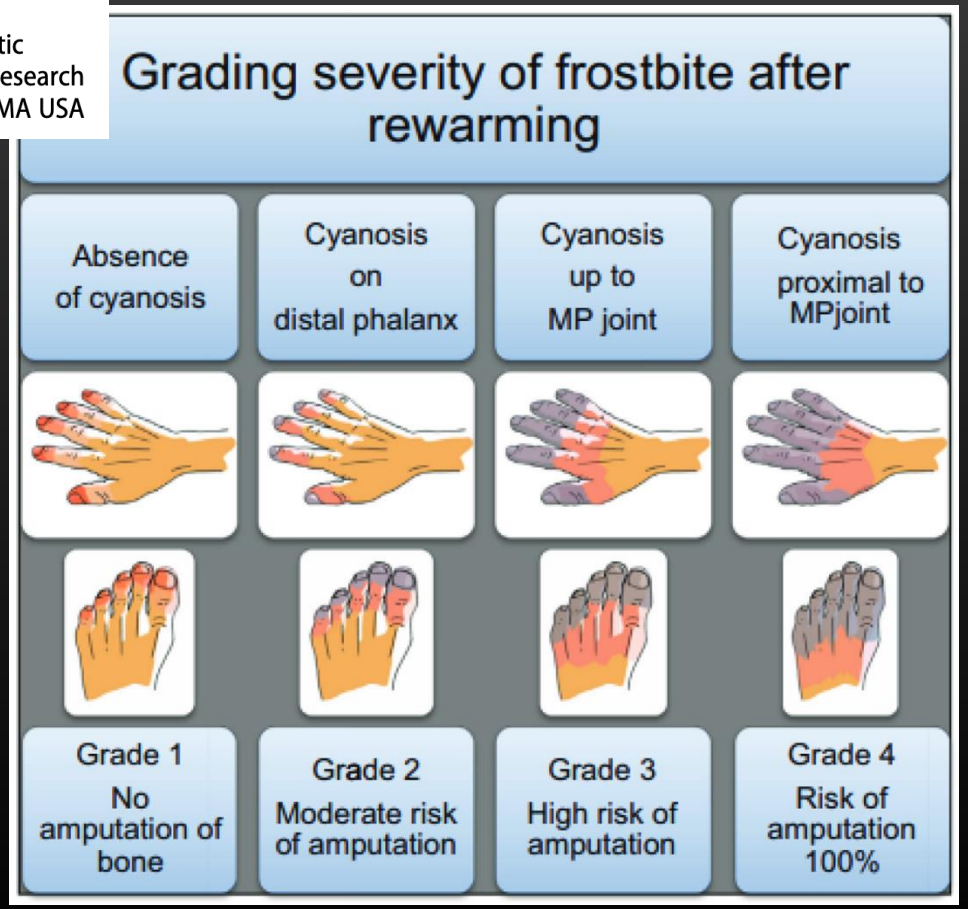
Arne Johan Norheim [a], Wendy Sullivan-Kwantes [c], Tuva Steinberg [a,b], John Castellani [d] and Karl E. Friedl [d]

[a]National Research Center in Complementary and Alternative Medicine (NAFKAM), Institute of Community Medicine, UiT- The Arctic University of Norway, Tromsø, Norway; [b]Norwegian Armed Forces - Joint Medical Service, Norway; [c]Joint medical services, Defence Research and Development Canada-Toronto Research Center, Sessvollmoen; [d]U.S. Army Research Institute of Environmental Medicine, Natick MA USA

Scores based on Injury/Symptoms
(i.e. Superficial/Severe or Degree)

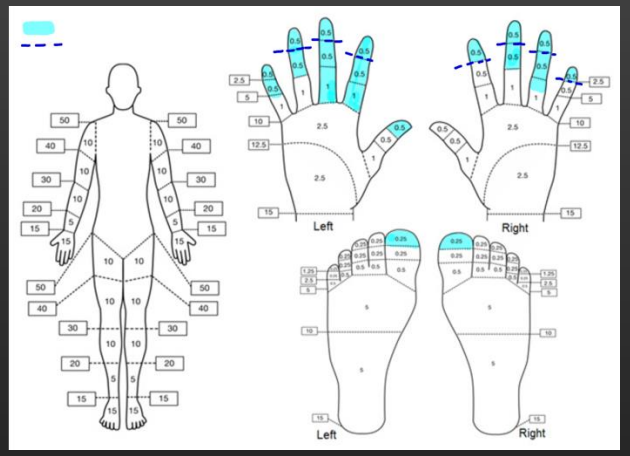
$\neq$

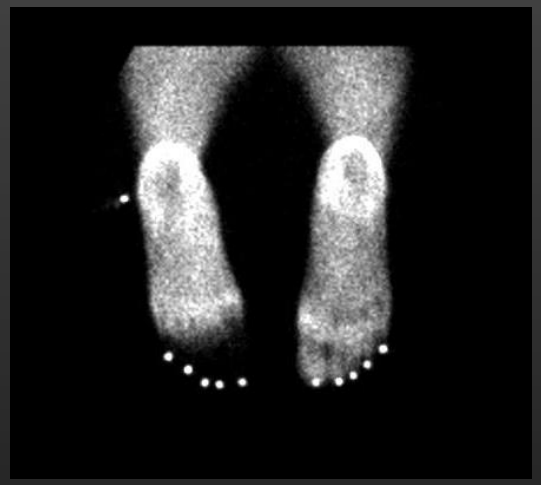
Outcome Grade
(Cauchy Frostbite Grade)



Cauchy et al. 2016

Visual Assessment of Severity Lack Reliability





No significant correlations were found between amputation level and clinical assessment

- admission (r = -0.08, p =0.729)
- day 3 (r = 0.18, p = 0.459)
- discharge (r = 0.26, p = 0.260).

Wilderness and Environmental Medicine, **12**, 248–255 (2001)

ORIGINAL RESEARCH

Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme

EMMANUEL CAUCHY, MD; ERIC CHETAILLE, MD; VINCENT MARCHAND, MD; BERNARD MARSIGNY, MD

From the Department of Mountain Medicine and Trauma, Chamonix Hospital, Chamonix, France.

THE INITIAL LESION

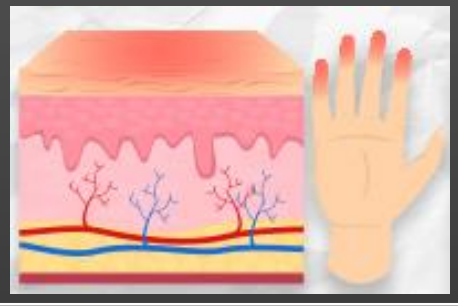
The initial lesion at hospitalization was characterized by cyanosis and grayness in color, which extended from the digit tip in a centripetal, ascending character toward the base of the limb. This aspect persisted despite rapid rewarming and was accompanied by anesthesia. In the study group, there were no blisters within 12 hours of beginning rewarming, except in 1 case with associated skin trauma (related to use of the hands to build a snow cave). For a few cases, the lesion was more heterogeneous with associated edema. The limit of the initial lesion was usually quite well demarcated just after initial treatment.

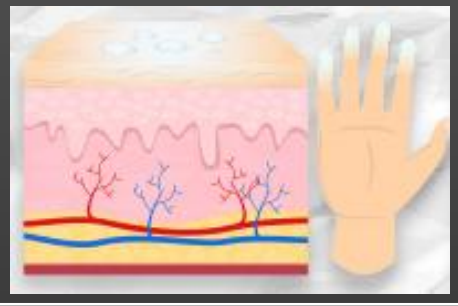
Table 1. Probability of amputation based on the extent of the initial lesion

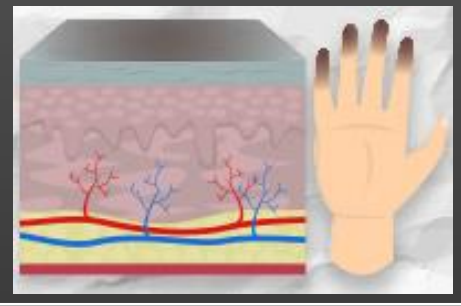
	Extent (level of involvement)	*Probability of bone amputation (95% CI)*
Hand	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	100
	3 (proximal phalanx)	83 (66; 100)
	2 (intermediary phalanx)	39 (25; 52)
	1 (distal phalanx)	1 (00; 03)
Foot	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	98 (93; 100)
	3 (proximal phalanx)	60 (45; 74)
	2 (intermediary phalanx)	23 (10; 35)
	1 (distal phalanx)	0
Hand and foot	5 (carpal/tarsal)	100
	4 (metacarpal/metatarsal)	98 (95, 100)
	3 (proximal phalanx)	67 (55; 79)
	2 (intermediary phalanx)	31 (22; 41)
	1 (distal phalanx)	1 (00; 02)

Specificity ~ 30%

No correlation of treatment with final amputation







Pulses	Present	Reduced	Absent	Absent	
Perfusion Imaging	Present	Variable	Reduced to Absent	Absent	
Color*	Darkened/reddish skin, white patches	Discolored skin	Bluish/white	Bluish/black	Necrosis
Blister**	No blisters	Blisters with clear fluid	Clear and Hemorrhagic	Clear and Hemorrhagic	
Lesion**	No lesions	Present	Present	Present	
Sensation/ Pain***	Intense	Reduced	Absent	Absent	

Cauchy	Grade 1	Grade 2	Grade 3	Grade 4
Degree	1st	2nd	3rd	4th
	Superficial		Severe	

* Melanin level in skin will impact visual appearance
**Blisters/Lesions may not be present immediately after rewarming
***Rewarming is very painful, sensation is absent in areas of severe frostbite injury. Surrounding tissue typically has partial thickness injuries (lessor grade/severity more proximal)

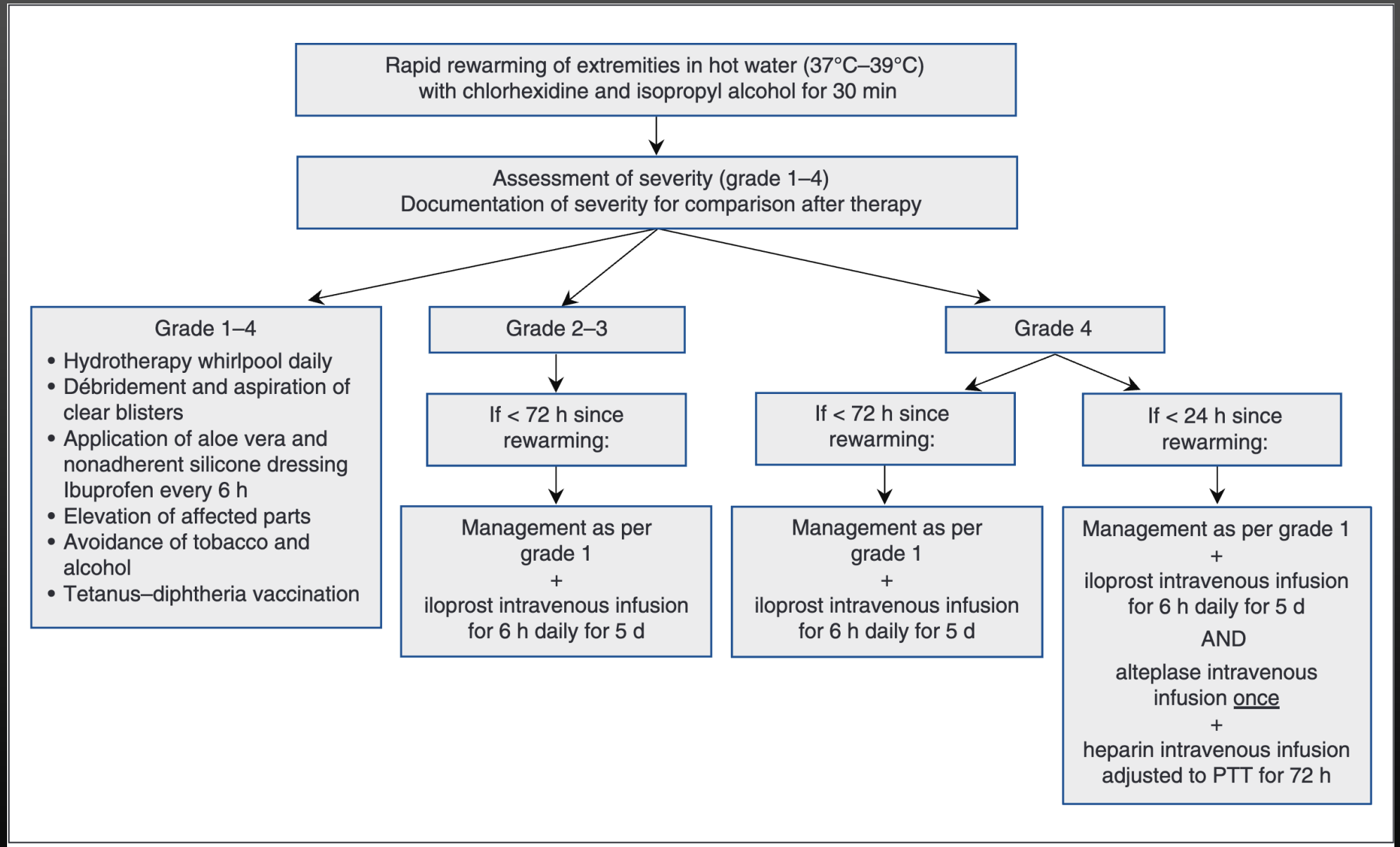


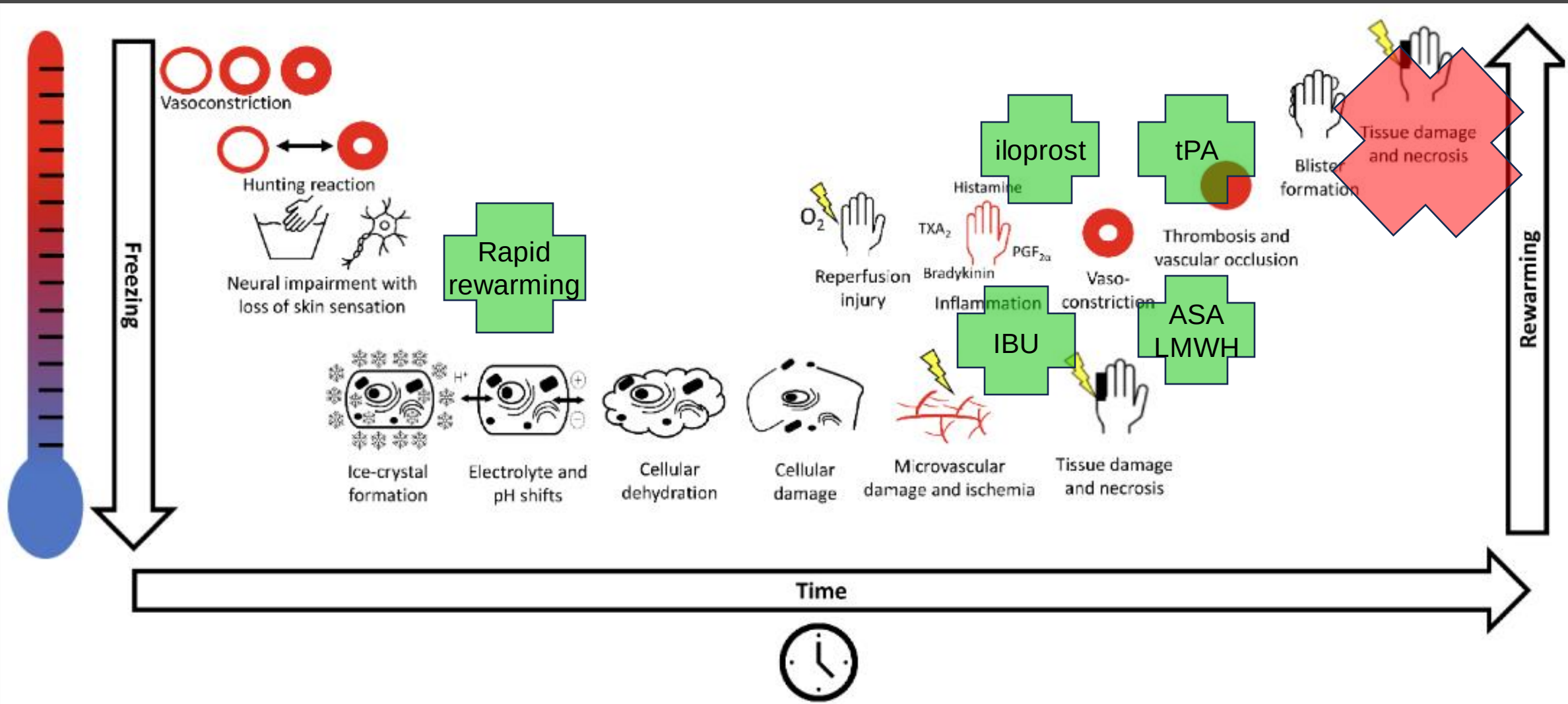
Figure 1: Yukon Frostbite Protocol. Note: PTT = partial thromboplastin time.

Poole, A., Gauthier, J. & MacLennan, M. Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. *CMAJ Open* **9**, E585–E591 (2021).

Specific Aim 2: To assess the utility and accuracy of visual assessment of frostbite injury compared to formal perfusion imaging and outcome

Intervention Goals

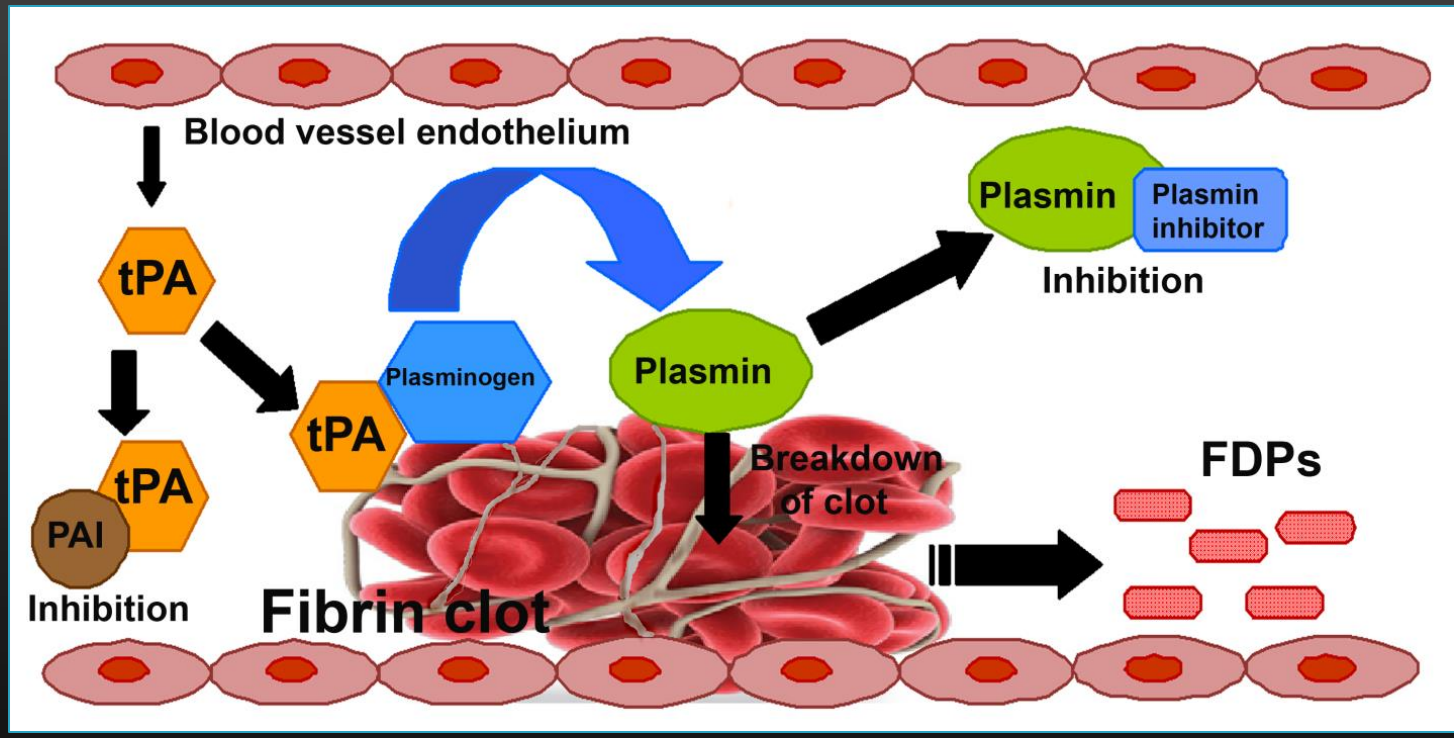
- Primary Goals:
  - Prevent tissue ischemia.
  - Mitigate inflammation.
  - Restore circulation and protect tissue.
- Interventions Overview:
  - Thrombolytics
  - Iloprost
  - Anti-thrombotics (anti-coags/anti-platelets)
  - Anti-inflammatory (ibuprofen)



Regli, I.B.; Strapazzon, G.; Falla, M.; Oberhammer, R.; Brugger, H. Long-Term Sequelae of Frostbite—A Scoping Review. Int. J. Environ. Res. Public Health 2021, 18, 9655. https://doi.org/10.3390/ijerph18189655

Thrombolytics – Tissue Plasminogen Activator (tPA)

- Effect: Breaks down blood clots in frostbite-affected tissues, restoring blood flow and oxygen delivery to the extremities.
- Clinical Impact:
  - Shown to significantly reduce amputation rates when used within 24 hours.



Bhattacharjee, Payel, and Debasish Bhattacharyya. "An insight into the abnormal fibrin clots—its pathophysiological roles." Fibrinolysis and Thrombolysis (2014): 1-29.

Summary patients treated with and without thrombolytics and resulting salvage rate

Author	Year	Total Number of Patients	Number of Patients Treated with tPA	Delivery Route	Imaging	Digit, segment, or overall Salvage tPA*	Weighted Averages tPA	Digit, segment, or overall Salvage no tPA/adjuvant therapy alone*
Twomey	2005	6	6	IA	Angio	50		-
Bruen	2007	32				90		49
Taveri	2016	13				83		-
Gonzaga	2016	69				68.6		unk
Linford	2017	14				81.1		unk
Patel	2017	17				85		23
Al Yafi	2019	18				44.4		33.3
Paine	2020	17				80		unk
Heard	2020	99				82		64.3
Heard	2020	3				100		-
Twomey	2005	13				81		-
Cauchy	2011	47				96.9		-
Johnson	2011	11				60.9		-
Jones	2017	15				72.5		unk
Nygaard	2017	73				74		55
Wexler	2017	6				75.4		-
Lacey	2021	165				84.6		54.3
Carmichael	2021	199				68.1		59.8
Poole**	2021	22	5	IV+iloprost	None	50		-
IA		**285**	**125**			**73.8**	**76.7**	
IV		**532**	**302**			**79.3**	**77.1**	
Total		**817**	**427**			**76.5**	**77**	**46.5**

Amputation Rate
23% tPA
54% no tPA

Abbreviations: h, hours; IA, intra-arterial; IV, intravascular; tPA, thrombolytics; unk, unknown.

Summary patients treated with and without thrombolytics and resulting salvage rate

Author		Total Number	Number of Patients Treated with			Digit, segment, or overall Salvage tPA*	Weighted Averages tPA	Digit, segment, or overall Salvage no tPA/adjuvant therapy alone*
Twomey						50		-
Bruen						90		49
Taveri						83		-
Gonzaga						68.6		unk
Linford						81.1		unk
Patel						85		23
Al Yafi						44.4		33.3
Paine						80		unk
Heard						82		64.3
Heard						100		-
Twomey						81		-
Cauchy						96.9		-
Johnson	2011	11	11	IV	Tc99	60.9		-
Jones	2017	15	12	IV	[illegible]99	72.5		unk
Nygaard	2017	73	45	IV	T[illegible]9	74		55
Wexler	2017	6	6	IV	Non[illegible]	75.4		-
Lacey	2021	165	125	IV	Tc99 & M[illegible]	84.6		54.3
Carmichael	2021	199	72	IV	Visual & Tc9[illegible]	68.1		59.8
Poole**	2021	22	5	IV+iloprost	None	50		-
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IV		**532**	**302**			**79.3**	**77.1**	
Total		**817**	**427**			**76.5**	**77**	**46.5**

Amputation Rate
IA 23.3%
IV 22.9%

Abbreviations: h, hours; IA, intra-arterial; IV, intravascular; tPA, thrombolytics; unk, unknown.

Time Is Tissue

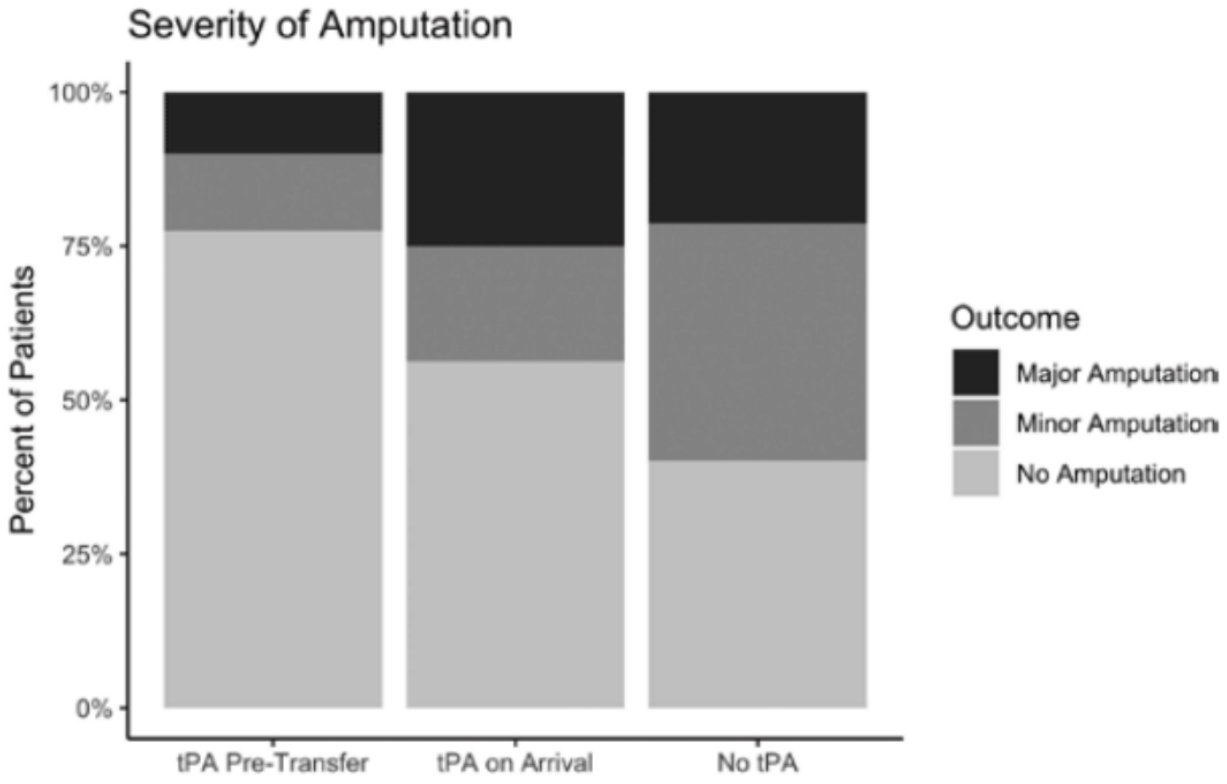
- Every hour delay 28% decrease in salvage
  - Remote Thrombolytic Role
    - 2.3% complication (N=2)
    - Efficacious (OR 0.19, 0.05-0.65)

- Earlier delivery -> better outcomes

Guidelines for Thrombolytic Therapy for Frostbite

Sean Hickey*, Amy Whitson†, Larry Jones†, Lucy Wibbenmeyer‡, Colleen Ryan||, Ryan Fey§, Jeffrey Litt¶, Renata Fabia**, Lee Cancio††, William Mohr‡‡,||||, John Twomey§§, Anne Wagner¶¶, Amalia Cochran†,, J. Kevin Bailey***,

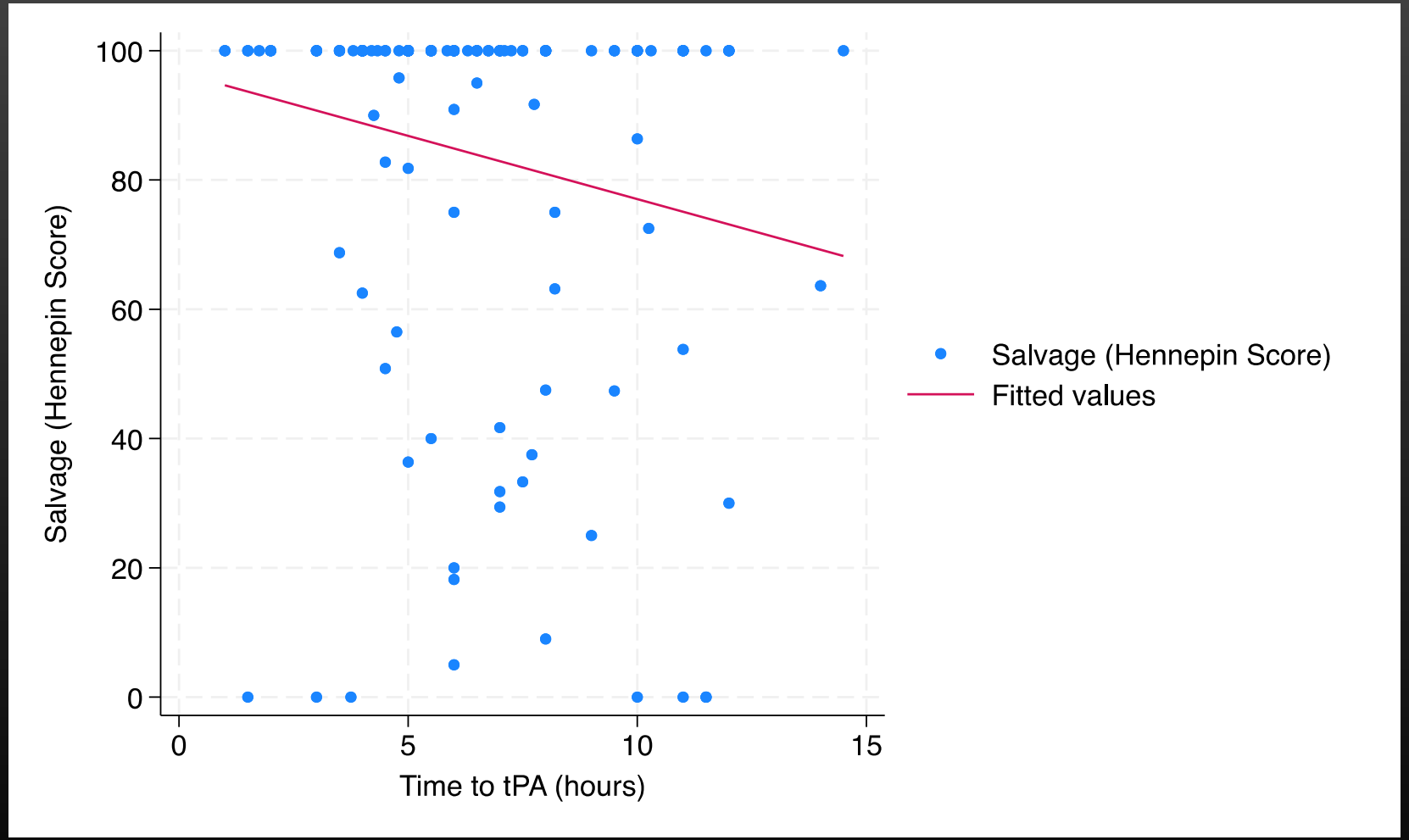
The data are insufficient to support standardized treatment of all patients with frostbite with thrombolytic therapy. The following guidelines, however, should be applied to all patients with cyanosis persisting proximal to the distal phalanx (Grade 3 or 4 frostbite injury) and demonstrated loss of perfusion at or proximal to the middle phalanx immediately after rewarming.



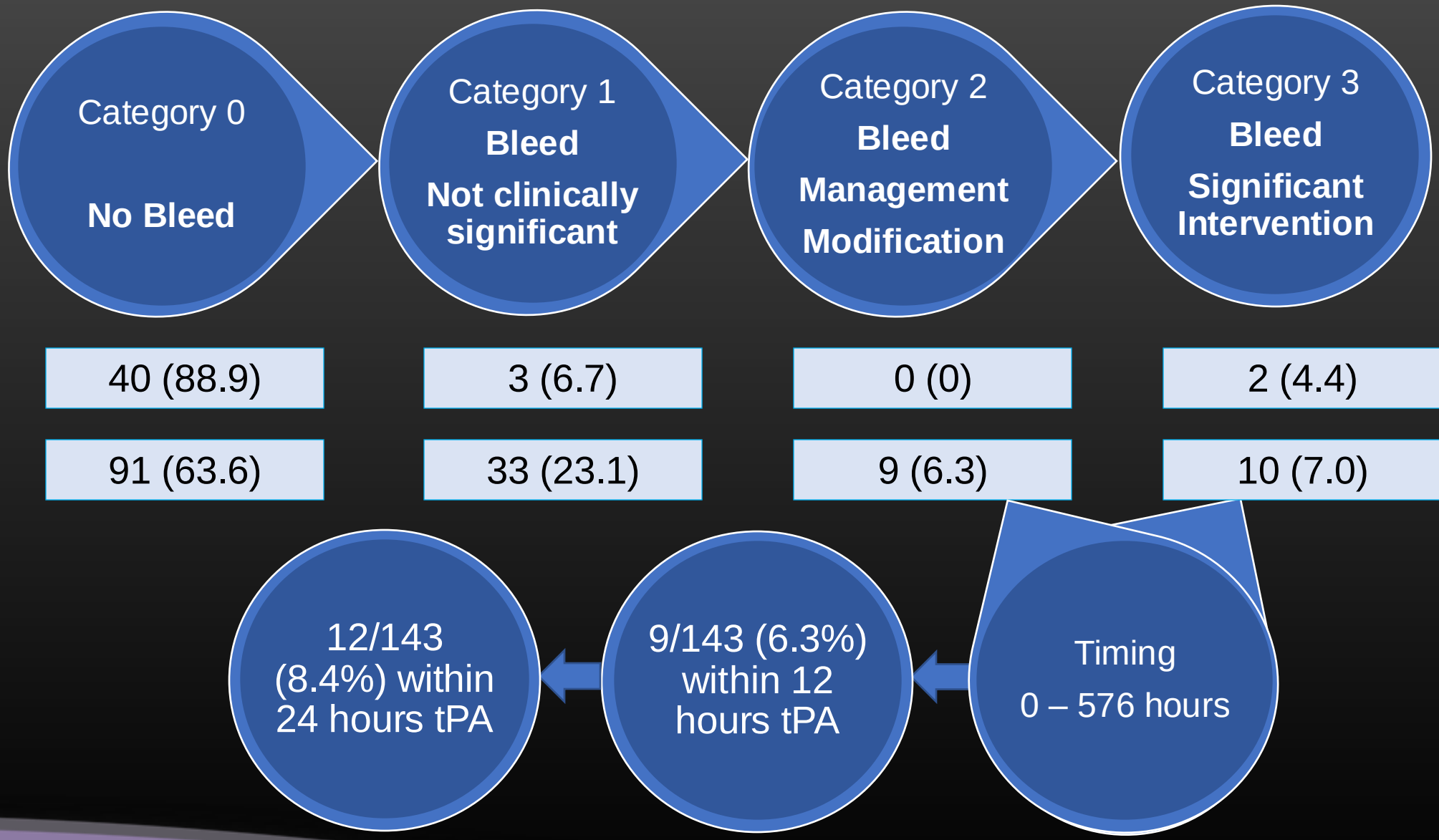
Nygaard RM, Lacey AM, Lemere A, Dole M, Gayken JR, Lambert Wagner AL, Fey RM. Time Matters in Severe Frostbite: Assessment of Limb/Digit Salvage on the Individual Patient Level. J Burn Care Res. 2017
Carmichael H, Michel S, Smith TM, Duffy PS, Wiktor AJ, Lambert Wagner A. Remote Delivery of Thrombolytics 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

Time Is Tissue, but

…treatment can be effective out to a wider range of times.



Bleeding complications in severe frostbite



	Category 0	Category 1	Category 2	Category 3
No tPA	40 (88.9)	3 (6.7)	0 (0)	2 (4.4)
tPA	91 (63.6)	33 (23.1)	9 (6.3)	10 (7.0)

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Murphy JE, Winters MK, Rogers C, Walter E, Neumann N, Weber L, Lacey AM, Punjabi G, Endorf FW, Nygaard RM. Bleeding Complications in Patients With Severe Frostbite Injury. *J. Burn Care Res.* **44**, 745–750 (2022).

Vasodilators – Iloprost

- Mechanism of Action: Iloprost is a prostacyclin analog that acts on prostaglandin I2 (PGI2) receptors
  - inhibits platelet aggregation and causes vasodilation

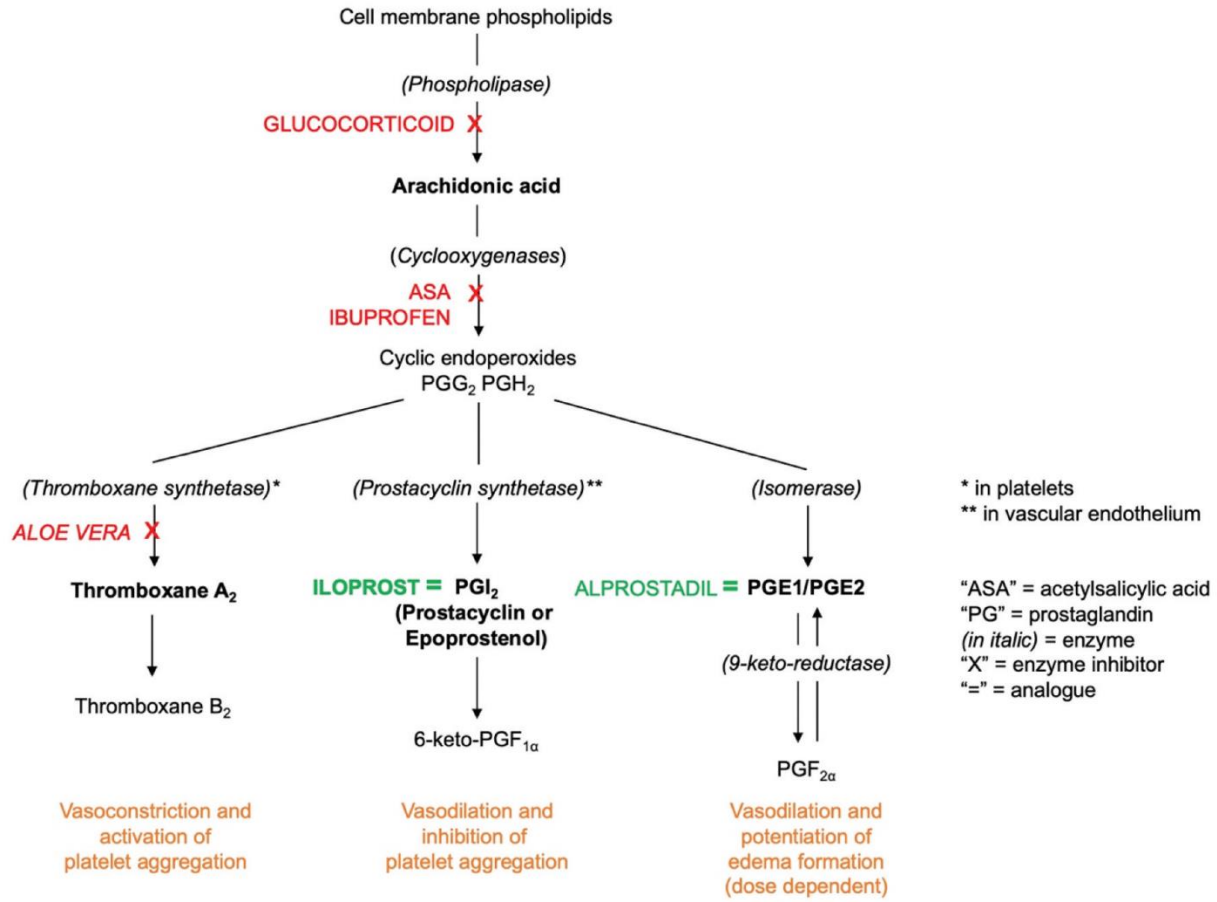

Figure 1. Conversion of arachidonic acid to thromboxane and prostaglandins and their known analogues, inhibitors and roles (adapted from references 8, 22, 23 and 24).

Josianne Gauthier, Dunavan Morris-Janzen & Alexander Poole (2023) Iloprost for the treatment of frostbite: a scoping review, International Journal of Circumpolar Health, 82:1, 2189552, DOI: 10.1080/22423982.2023.2189552

INTERNATIONAL JOURNAL OF CIRCUMPOLAR HEALTH
2023, VOL. 82, 2189552
https://doi.org/10.1080/22423982.2023.2189552

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Iloprost for the treatment of frostbite: a scoping review

Josianne Gauthier[a], Dunavan Morris-Janzen[b] and Alexander Poole[a,c]

[a]Whitehorse General Hospital, Yukon Hospital Corporation, Whitehorse, Yukon, Canada; [b]Northern Medical Program, University of British Columbia, Prince George, British Columbia, Canada; [c]Department of Surgery, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

Table 1. Overall characteristics of included studies.

Included Study	Country	Study Design	Number of patients treated with iloprost	Percentage of male patients	Patient age, mean	Predisposing event	Frostbite severity	Number of digits affected
Groechenig **1994** [21]	Austria	Case report	5	80%	35	Sport, substance use, paralysis	2nd and 3rd degree	-
Hödl **2005** [38] [German]	Austria	Case report	2	100%	37	Sport	1st, 2nd and 3rd degree	20
Roche-Nagle et al. **2008** [39]	Ireland	Case report	1	100%	47	Homelessness, substance use	Severe	10
Imray et al. **2009** [40]	England	Case report	1	-	n/a	Sport	-	8
Cauchy et al. **2011** [41]	France	Randomised controlled trial	32	100%	32	Sport	Stage 2–4	301
Gorjanc et al. **2012** [42] [Slovenian]	Slovenia	Case series	7	-	n/a	Sport	Deep	-
Haik J et al. **2016** [43]	Nepal, Israel	Case series	4	75%	30	Sport	Grade 1–4	-
Cauchy et al. **2016** [44] (Abstract)	France	Case series (iloprost versus other therapies)	78	-	-	-	Grade 2–4	-
Poole & Gauthier **2016** [45]	Canada	Case report	2	100%	45	Sport	Grade 3	10
Lindford et al. **2017** [46]	Finland	Case series	4	-	-	n/a	Severe	n/a
Pandey et al. **2018** [47]	Nepal	Case series	5	100%	39	Sport	Grade 2–4	34
Gorjanc et al. **2018** [48] (Abstract)	Slovenia	Case report	2	100%	25	Sport	Deep	-
Irarrazaval et al. **2018** [49]	Nepal	Case report	1	100%	60	Sport	Grade 2 and 3	5
Jud et al. **2019** [50]	Austria	Case report	1	100%	45	Sport	Grade 2	-
Lorenzo-Villalba et al. **2021** [51]	France	Case report	1	0%	83	Chronic disease (Cold Agglutinin Disease)	-	-
Poole et al. **2021** [52]	Canada	Case series	22	77%	39	Sport, substance use, car trouble, work, psychiatric disorder	Grade 2–4	142
MacLennan et al. **2021** [53]	Canada	Case report	1	100%	48	Car trouble	Grade 2	1
Magnan et al. **2021** [54]	Switzerland, France	Prospective single-arm study	58	93%	33	Sport, work, homelessness	Grade 3 and 4	238
Magnan et al. **2022** [55]	Switzerland	Case report	1	100%	36	Sport	Grade 3	10
Crooks et al. **2022** [56]	Canada	Case series (iloprost versus standard of care)	26	89%	36	Substance use, car trouble, work, sport, unknown	Grade 2–4	242
All studies	n/a	n/a	**254**	88%	**42**	n/a	n/a	**>1000**

"-"= information not available, "n/a"= not applicable.

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Table 3. Relevant outcome data extracted.

Included Study	Outcome measured	Outcome	Adverse drug event
Groechenig **1994** [21]	Patients requiring amputation	0/5 (0%)	-
Hödl **2005** [38]	Affected digits requiring amputation	5/20 (25%)	None
Roche-Nagle et al. **2008** [39]	Affected limbs requiring amputation	2/2 (100%)	-
Imray et al. **2009** [40]	Affected digits appearance and function	Full function regained	-
Cauchy et al. **2011** [41]	Risk of patient requiring amputation based on bone scan at day 8	0/16 (0%) iloprost 3/16 (19%) iloprost + alteplase	Hot flashes (55%), nausea (25%), palpitation (15%), vomiting (5%)
	Affected digits requiring amputation according to treatment	0/142 (0%) iloprost 5/159 (3%) iloprost + alteplase	
	Affected digits requiring amputation according to severity of frostbite	Stage 2 Stage 3 Stage 4 0/64 (0%) 0/74 (0%) 0/3 (0%) iloprost	
	Affected digits req according to tim		
Gorjanc et al. **2012** [42]	Patients requiring		Dizziness and hypotension requiring discontinuation of iloprost (29%)
Haik J et al. **2016** [43]	Patients requiring		-
Cauchy et al. **2016** [44]	Patients requiring according to sev		-
Poole & Gauthier **2016** [45]	Affected digits req		None
Lindford et al. **2017** [46]	Overall digital salv		None
Pandey et al. **2018** [47]	Affected digits req		Headache (40%), nausea (40%), hypotension requiring dose reduction (20%)
Gorjanc et al. **2018** [48]	n/a		-
Irarrazaval et al. **2018** [49]	Affected digits req		-
Jud et al. **2019** [50]	Patient requiring a		-
Lorenzo-Villalba et al. **2021** [51]	Affected limbs req		Hypotension and headache limiting dose increase (100%)
Poole et al. **2021** [52]	Patients requiring Affected digits req according to sev		Headache (50%), flushing (36%), tachycardia (36%), nausea (27%), vomiting (9%), dizziness (9%), hypotension (4%), bleeding (4%)
MacLennan et al. **2021** [53]	Visual microvascul and treatment r		None
Magnan et al. **2021** [54]	Preserved segment (mean) compare Amputated rays*** historical group	2 iloprost alone	-
Magnan et al. **2022** [55]	Affected digits requiring amputation	0/10 (0%)	-
Crooks et al. **2022** [56]	Affected digits requiring amputation according to frostbite severity compared to standard care	Grade 2 Grade 3 Grade 4 0/44 (0%) 18/102 (18%) 44/96 (46%)	Tachycardia requiring dose reduction (12%), headache (8%), headache requiring iloprost discontinuation (4%)

"-" = information not available
* Calculated using the total number of digits at risk minus number of digits amputated divided by total number of digits at risk multiplied by 100
** Each phalanx and each metacarpal or metatarsal is defined as a segment. Preserved segments was defined as the difference between the number of segments with frostbite and lost segments
*** 4 segments comprise a ray (3 segments for the thumb or the hallux)

Overall amputation rate following iloprost ranges from 0-100%, but most showed improvement

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Josianne Gauthier, Dunavan Morris-Janzen & Alexander Poole (2023) Iloprost for the treatment of frostbite: a scoping review, International Journal of Circumpolar Health, 82:1, 2189552, DOI: 10.1080/22423982.2023.2189552

Table 3. Relevant outcome data extracted.

Included Study	Outcome measured	Outcome	Adverse drug event
Groechenig **1994** [21]	Patients requiring amputation	0/5 (0%)	-
Hödl **2005** [38]	Affected digits requiring amputation	5/20 (25%)	None
Roche-Nagle et al. **2008** [39]	Affected limbs requiring amputation	2/2 (100%)	-
Imray et al. **2009** [40]	Affected digits appearance and function	Full function regained	-
Cauchy et al. **2011** [41]	Risk of patient requiring amputation based on bone scan at day 8	0/16 (0%) iloprost 3/16 (19%) iloprost + alteplase	Hot flashes (55%), nausea (25%), palpitation (15%), vomiting (5%)
	Affected digits requiring amputation according to treatment	0/142 (0%) iloprost 5/159 (3%) iloprost + alteplase	
	Affected digits requiring amputation according to sev	Stage 2 Stage 3 Stage 4	
	Affected digits req according to tim		
Gorjanc et al. **2012** [42]	Pati uiring		Dizziness and hypotension requiring discontinuation of iloprost (29%)
Haik J et al. **2016** [43]	Pa ents requiring		-
Cauchy et al. **2016** [44]	P ients requiring according to sev		-
Poole & Gauthier **2016** [45]	Affected digits req		None
Lindford et al. **2017** [46]	Overall digital salva		None
Pandey et al. **2018** [47]	Affected digits req		Headache (40%), nausea (40%), hypotension requiring dose reduction (20%)
Gorjanc et al. **2018** [48]	n/a		-
Irarrazaval et al. **2018** [49]	Affected digits req		-
Jud et al. **2019** [50]	Patient requiring a		-
Lorenzo-Villalba et al. **2021** [51]	Affected limbs req		Hypotension and headache limiting dose increase (100%)
Poole et al. **2021** [52]	Patients requiring		Headache (50%), flushing (36%), tachycardia (36%), nausea (27%), vomiting (9%), dizziness (9%), hypotension (4%), bleeding (4%)
	Affected digits req according to sev		
MacLennan et al. **2021** [53]	Visual microvascula and treatment r		None
Magnan et al. **2021** [54]	Preserved segment (mean) compare		-
	Amputated rays*** compared to historical group	0 iloprost + HBOT 2 iloprost alone	
Magnan et al. **2022** [55]	Affected digits requiring amputation	0/10 (0%)	-
Crooks et al. **2022** [56]	Affected digits requiring amputation according to frostbite severity compared to standard care	Grade 2 Grade 3 Grade 4 0/44 (0%) 18/102 (18%) 44/96 (46%)	Tachycardia requiring dose reduction (12%), headache (8%), headache requiring iloprost discontinuation (4%)

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* Calculated using the total number of digits at risk minus number of digits amputated divided by total number of digits at risk multiplied by 100
** Each phalanx and each metacarpal or metatarsal is defined as a segment. Preserved segments was defined as the difference between the number of segments with frostbite and lost segments
*** 4 segments comprise a ray (3 segments for the thumb or the hallux)

Close to U.S. frostbite population from published literature Amputation for severe injury from 18-46% treated with iloprost

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Josianne Gauthier, Dunavan Morris-Janzen & Alexander Poole (2023) Iloprost for the treatment of frostbite: a scoping review, International Journal of Circumpolar Health, 82:1, 2189552, DOI: 10.1080/22423982.2023.2189552

Specific Aim 3: To evaluate the impact of thrombolytics (and iloprost) on early tissue salvage.

Antithrombotic: Anticoagulants & Antiplatelets

TABLE 9-4 Frostbite Management: Drugs, Doses, and Modes of Action and Rationale*

Intervention	Dose	Action
★Aspirin	75-250 mg orally once daily	Antiplatelet agent, improve rheology
Ibuprofen	400 mg bid or tid orally	Antiprostaglandin effect
Aloe vera gel or cream	With dressing changes every 6 hr	Topical antiprostaglandin effect
Oxygen	2 L/min above 4000 m (13,123 ft) or when SpO_2 is below 90%	Improve tissue oxygenation
Hyperbaric oxygen therapy	2-2.5 atm 1-2 hr daily	Improve tissue oxygenation; improve rheology
Iloprost	2-10 mg/hr IV titrated against side effects	Vasodilator; improve rheology
Nitroglycerin	100 mcg IA single dose	Vasodilator
Papaverine	300 mg over 1 hr IA	Vasodilator
Reserpine	0.1 to 0.25 mg once daily	Vasodilator
Buflomedil	400 mg IV *or* 300 mg bid orally	Vasodilator; improve rheology
Pentoxifylline	400 mg tid orally for 2-6 weeks	Vasodilator; improve rheology
10% Dextran 40	20-mL bolus, 20 mL/hr IV	Improve rheology
t-PA	1 mg/hr IA or IV	Thrombolytic agent
★LMW heparin	Prophylactic dosage subcutaneously	DVT prevention; anticoagulant
	Therapeutic dosage subcutaneously	Maintain patency of recently thrombolysed vessels
Tetanus prophylaxis		

bid, Twice daily; *DVT*, deep vein thrombosis; *IA*, intraarterially; *IV*, intravenously; *LMW*, low-molecular-weight; *SpO_2*, oxygen saturation as measured by pulse oximetry; *tid*, three times daily; *t-PA*, tissue plasminogen activator.
*This table is intended to be used as a potential frostbite formulary reference, not as a protocol for treatment. See text for further discussion.

Freer, Luanne & Handford, Charles & Imray, Chris. (2016). Frostbite in Auerbach's Wilderness Medicine, 2-Volume Set, 7th Edition.

Anti-inflammatory Agents – Ibuprofen

Effect on Frostbite: Ibuprofen inhibits COX enzymes reducing production of prostaglandins

Popularized in the 80's – confirmatory studies needed

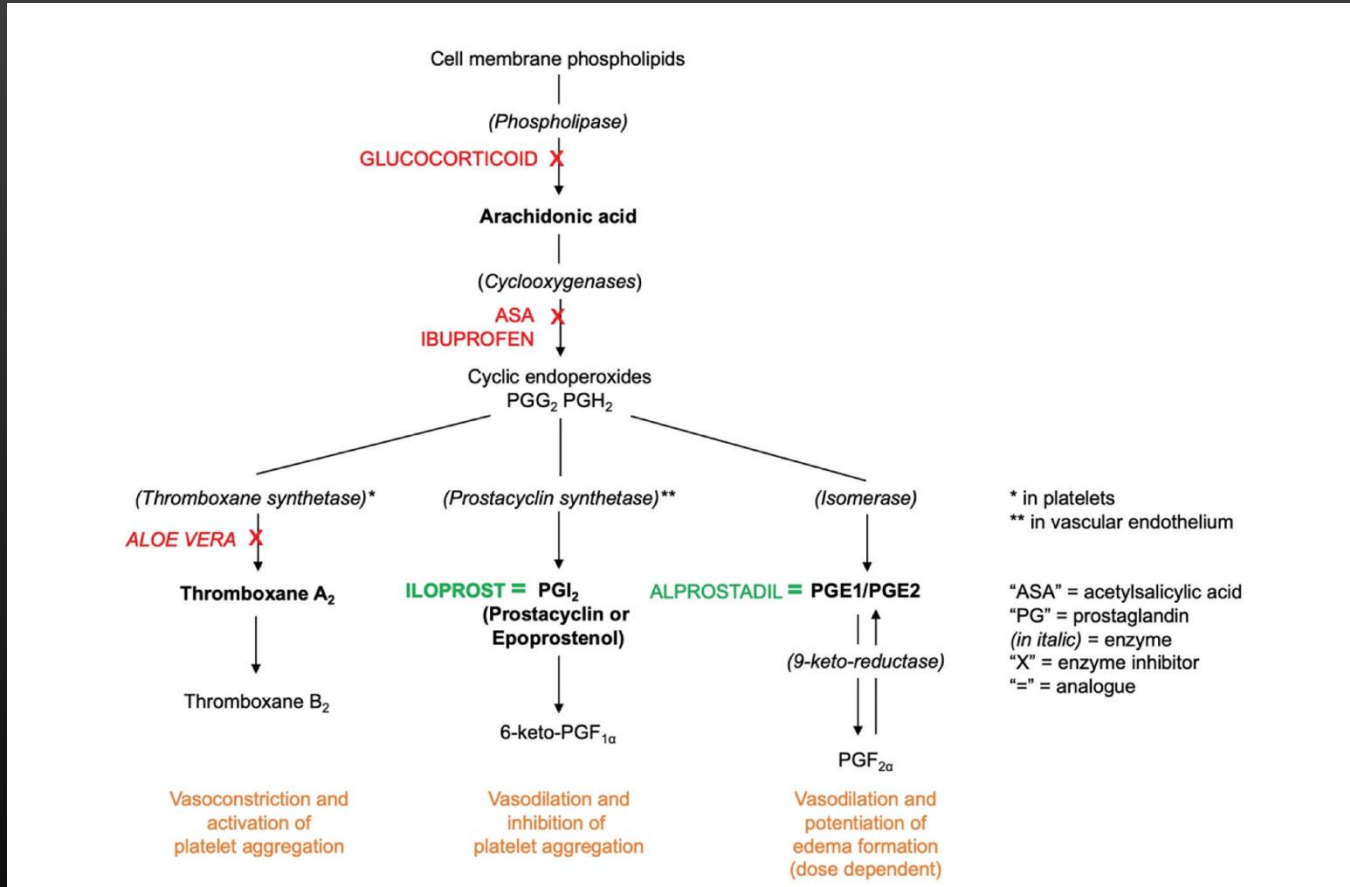
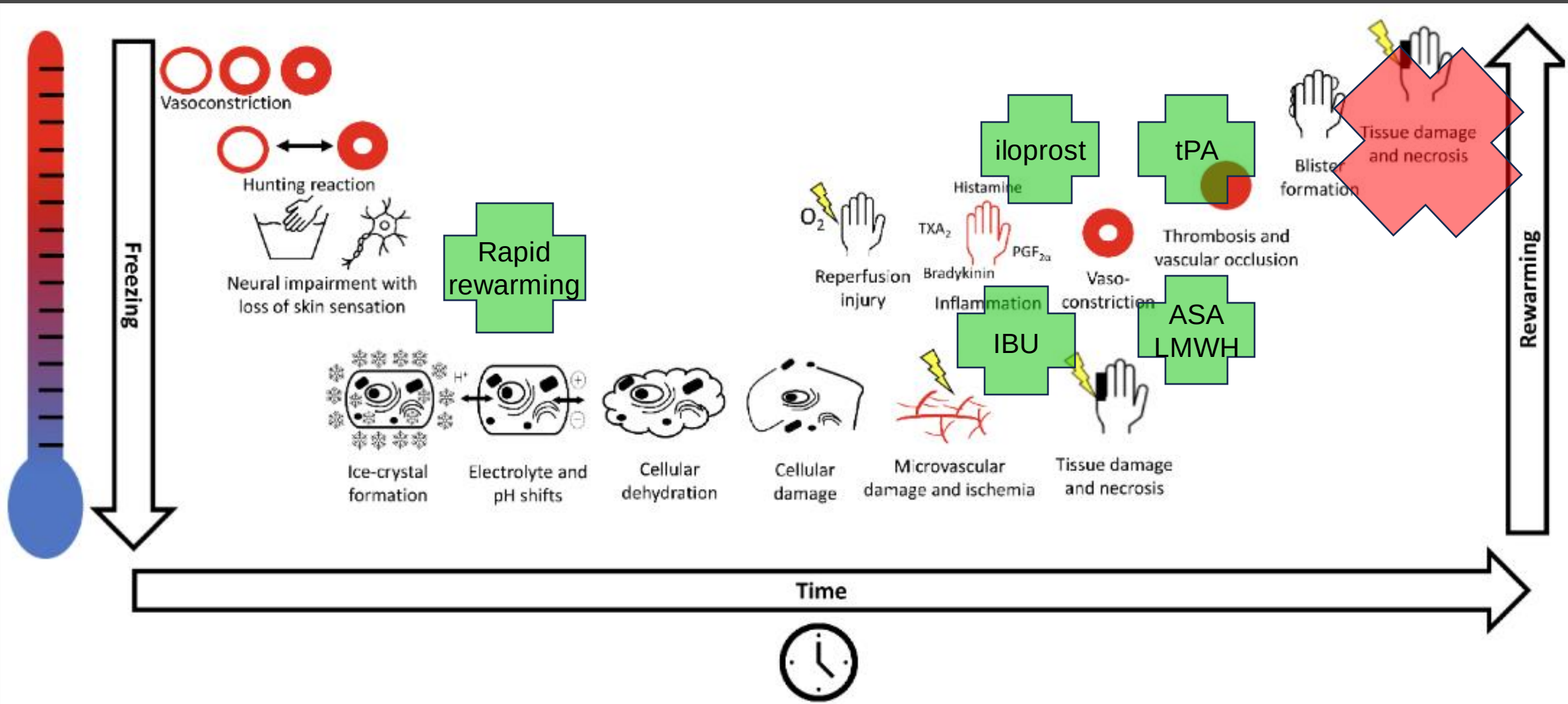


Figure 1. Conversion of arachidonic acid to thromboxane and prostaglandins and their known analogues, inhibitors and roles (adapted from references 8, 22, 23 and 24).

Josianne Gauthier, Dunavan Morris-Janzen & Alexander Poole (2023) Iloprost for the treatment of frostbite: a scoping review, International Journal of Circumpolar Health, 82:1, 2189552, DOI: 10.1080/22423982.2023.2189552



Regli, I.B.; Strapazzon, G.; Falla, M.; Oberhammer, R.; Brugger, H. Long-Term Sequelae of Frostbite—A Scoping Review. Int. J. Environ. Res. Public Health 2021, 18, 9655. https://doi.org/10.3390/ijerph18189655

Cold injury and polytrauma

National Inpatient Sample

Frostbite patients (N=8085)

- crush injuries (1%)
- fractures (4%)
- intracranial hemorrhage (3.7%)
- other wounds (3.8%)

Future

- Next year: first data from FROST multicenter study
  - tPA vs iloprost vs combination
  - Aspirin vs LMWH vs warfarin
  - Accuracy of visual assessment with perfusion imaging/grade

- Contact me if you'd like to participate in non-funded substudy evaluating frostbite injury at the extremes of age

Email: Rachel.Nygaard@hcmed.org
Frostbite.research@gmail.com

My backyard 4/1/2023

FROST
MULTICENTER STUDY

Hennepin Healthcare

Department of Surgery

HennepinHealthcare

Cold ischemia time >> warm ischemia time

Effect of Rapid and Prolonged Rewarming on Local Cold Injury[1]

Josef Pichotka, *M. D.*

Robert B. Lewis, *Lieutenant Colonel, U. S. A. F. (MC)*

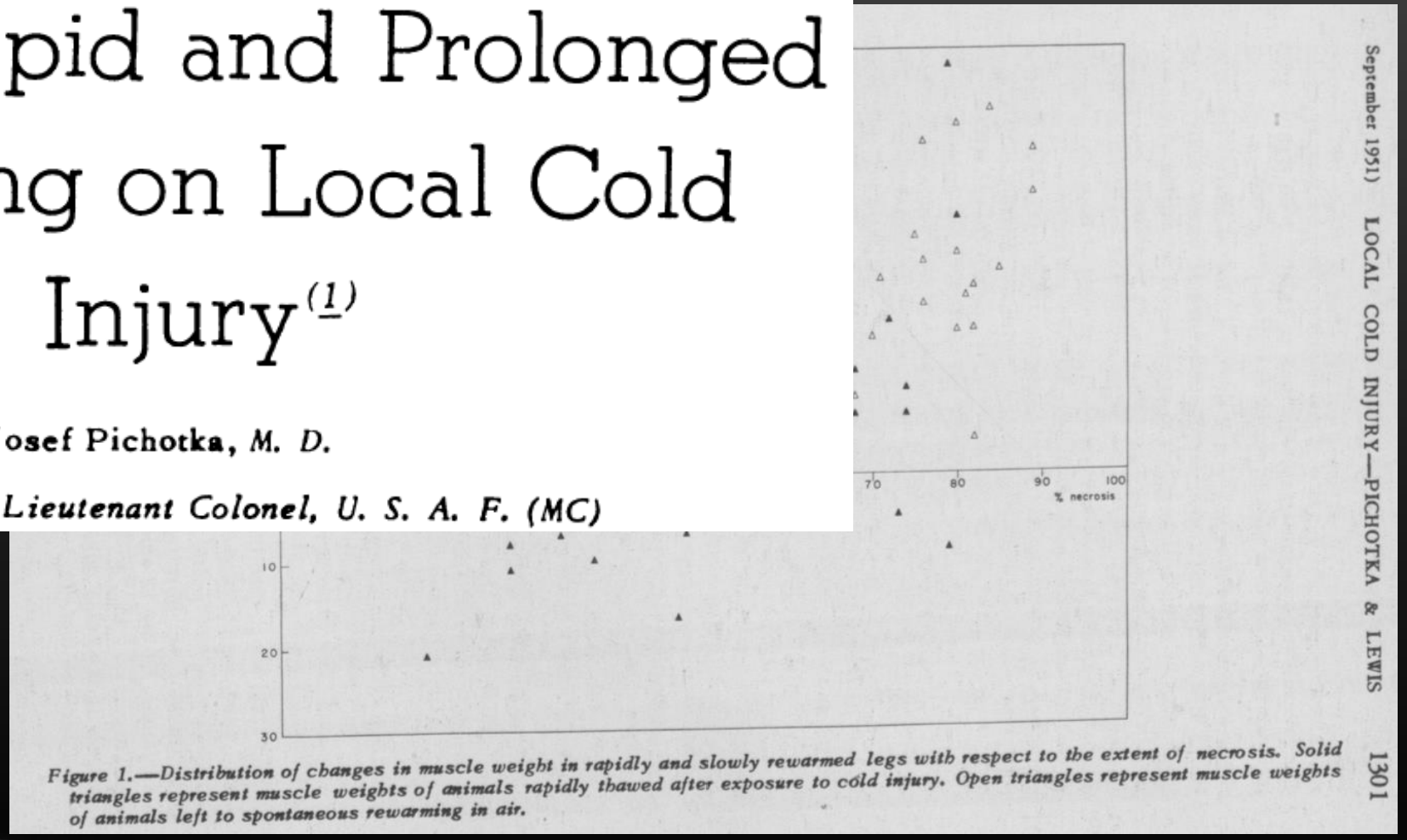
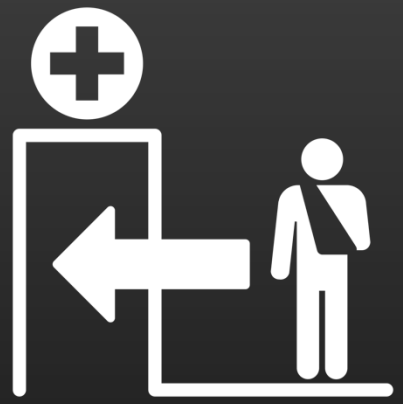


Figure 1.—Distribution of changes in muscle weight in rapidly and slowly rewarmed legs with respect to the extent of necrosis. Solid triangles represent muscle weights of animals rapidly thawed after exposure to cold injury. Open triangles represent muscle weights of animals left to spontaneous rewarming in air.

Complications associated with frostbite



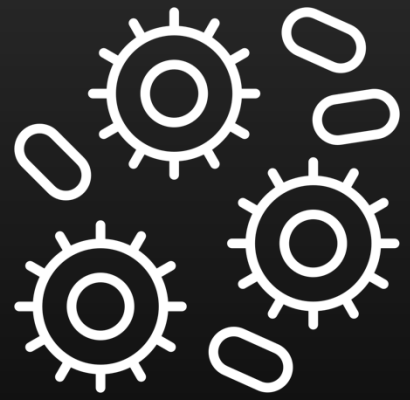
Unplanned readmission N=842

Complications N=452 (53.7%)

Amputation

Non-healing wound

Infection or Cellulitis



Endorf FW, Nygaard RM. High Cost and Resource Utilization of Frostbite Readmissions in the United States. J Burn Care Res. 2021
Shenaq DS, Beederman M, O'Connor A, Teele M, Robinson MR, Gottlieb LJ. Urban Frostbite: Strategies for Limb Salvage. J Burn Care Res. 2019
Urschel JD. Frostbite: predisposing factors and predictors of poor outcome. J Trauma. 1990
Valnicek SM, Chasmar LR, Clapson JB. Frostbite in the prairies: a 12-year review. Plast Reconstr Surg. 1993

Revision Surgery

Frostbite
13 (24%)

Infection or Cellulitis
6 (38%)

Debridement Alone
5 (31%)

Amputation Alone
6 (38%)

Both
5 (31%)

Coward A, Endorf FW, Nygaard RM. Revision Surgery Following Severe Frostbite Injury Compared to Similar Hand and Foot Burns. J Burn Care Res. 2022

Long-term outcomes

International Journal of
Environmental Research and Public Health

MDPI

Review

Long-Term Sequelae of Frostbite—A Scoping Review

Ivo B. Regli [1,2,*], Giacomo Strapazzon [1,3], Marika Falla [1,4], Rosmarie Oberhammer [5] and Hermann Brugger [1,3]

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2 Department of Anaesthesia and Intensive Care, "F. Tappeiner" Hospital, 39012 Merano, Italy
3 Department of Anaesthesia and Intensive Care, Medical University Innsbruck, 6020 Innsbruck, Austria
4 Center for Mind/Brain Sciences, University of Trento, 38123 Rovereto, Italy
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Among 493 patients from five studies,

341 (69%) had long term impairments.

Article	Population and Follow Up Timing	Frostbite Grade/Degree	Long-Term Sequelae
Norheim et al., 2018 [15]	Self-reported data of 397 Norwegian soldiers in 2017 having suffered frostbite from 2010–2014	1–2	70 % with long-term sequelae 21% unable to work and undertake usual leisure activities
Carlsson et al., 2014 [16]	Self-reported data of 12 patients; 4 patients with hand frostbite, 6 patients with feet frostbite, and 2 patients with hand and feet frostbite; hand frostbite was followed-up after 4 month and 4 years, foot frostbite only after 4 years	1–2	4 months after frostbite of the hands (n = 6): 100% with discomfort when exposed to cold 67% with cold sensation 67% with white fingers/toes 4 years after frostbite of the hands (n = 6): 100% with discomfort when exposed to cold 83% with cold sensation 17% with white fingers/toes 4 years after frostbite of the feet (n = 8): 89% with discomfort when exposed to cold 100% with cold sensation 100% with white fingers/toes
Koljonen et al., 2004 [17]	Self-reported data form 14 patients with frostbite during the previous 7 years	Not specified	15% with daily, intolerable pain 50% chronic pain 50% with limitations in their social life 36% with poor emotional well being
Ervasti et al., 2000 [18]	Clinical examination of 30 patients with frostbite 4–11 years earlier	2	63% with sequelae of any kind 66% with increased tendency for vasospasm 53% with hypersensitivity to cold 40% with numbness of fingers 33% with declined sensitivity to touch 13% with lowered working ability
Arvesen et al., 1996 * [19]	Clinical examination of 40 Norwegian soldiers with frostbite in the previous 21–78 months; 16 with involvement of the hands and 24 with involvement of the feet	1–3	38% with disturbed sense of cold 38% with disturbed sense of heat 33% skin and nail dystrophia 20% with hyperhidrosis 18% with reduced light-touch perception 18% with reduced pain perceptions 10% with reduced blunt-touch perception 8% with pain on deep pressure5% with paraesthesia 3% with reduced muscle power
Rosen et al., 1991 * [20]	Self-reported data of 40 Norwegian soldiers with frostbite at least 2 years prior; 18 with involvement of the hands and 28 with involvement of the feet	1–3	Hands: 100% with cold hypersensitivity 50% with paraesthesia 61% with hypaesthesia 56% skin and nail dystrophia 44% with pain 6% with hyperaesthesia 6% with hyperhidrosis 6% with arthralgia Feet: 93% with cold hypersensitivity 64% skin and nail dystrophia 54% with pain 46% with paraesthesia 54% with hypaesthesia 14% with hyperhidrosis 11% with hyperaesthesia 7% pain when walking 4% with arthralgia
Taylor et al., 1989 [21]	40 US soldiers examined 6 months after frostbite	1–4	65% with neurovascular sequelae (cold sensitivity, paraesthesia, pain, and hyperaesthesia) 8% had to be reassigned to new functions due to symptom severity
			Self-reported sequelae in winter 71% with numbness 70% with pain 69% with cold feet 58% with abnormal colour 53% with hyperhidrosis 40% with pathology in joints

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Objectives

- Understanding frostbite
- Best practices
- Outcomes
- Future studies

Frostbite: a treatment guideline for prehospital treatment in a military environment

B L Turner,[1] T T.C.F van Dongen ,[2,3] R R Berendsen,[4] F J.M de Jong,[1] E L Endert,[1] R A van Hulst,[5] R Hoencamp[2,3,6,7]

Box 1 : Prehospital care summarised

1a: Prolonged field care summarised:
⇒ Check for life-threatening disorders and treat these first
⇒ Seek adequate shelter from the elements and prevent the victim from further cooling
⇒ Remove constrictive objects like rings, etc
⇒ Remove boots, change wet clothing. Keep in mind swelling may impair putting on boots later on
⇒ If warm water is not directly available, attempt rewarming limb in armpit or groin of companion for 10 min. When not improving, severe frostbite is likely and rapid rewarming in water should be initiated as soon as possible
⇒ In case of considerable risk of refreezing later; wrap affected limb in blanket and evacuate to base or medical facility
⇒ Without risk of refreezing; immediately start rapid rewarming and adjunctive therapy.
⇒ Start with ibuprofen, and if indicated give paracetamol as baseline analgesic with opioids as adjunctive therapy during rewarming limb
⇒ Rehydrate patient with warm oral fluids (0.5–1 L; if sufficiently conscious)
⇒ Evacuate to medical facility as soon as possible for further treatment
DO NOT:
⇒ Apply emollients
⇒ Rub affected limb with hands or snow
⇒ Apply direct dry heat
⇒ Allow the patient to smoke

1b: Professional prehospital care summarised:
⇒ Check for life-threatening disorders and treat these first
⇒ Remove constrictive objects like rings, etc (if not done previously)
⇒ Place limb in warm water (37–42°C) until soft and red-purple colour reappears (usually 15–30 min)
⇒ Administer ibuprofen 400 mg orally every 8 hours
⇒ For pain control during rewarming consider administrating opiates: fentanyl transmucosal lollypop (Netherlands Armed Forces), morphine intravenous (IV) or esketamine IV
⇒ For pain control after rewarming: give paracetamol 1 g orally every 6 hours (max 4 g/day), increase ibuprofen to max. 600 mg every 6 hours (max 2400 mg/day)
⇒ Rehydrate; if sufficiently conscious give 0.5–1 L warm oral fluids, or warmed (37–42°C) IV fluids in 250 mL boluses until urine production normalises
⇒ Consider nifedipine 30–60 mg/day in three to six doses or iloprost
⇒ Provide basic wound and blister care, be careful with haemorrhagic blisters (see DO NOT)
⇒ Apply topical aloe vera
⇒ Apply bulky dressing (not circumferential!) and elevate limb
⇒ Evacuate to definitive care as soon as possible (preferably <24 hours) for enhanced therapeutic interventions
⇒ Routine use of antibiotics is not recommended, consider tetanus prophylaxis when skin is damaged and tetanus status is unknown
DO NOT:
⇒ Punctuate
⇒ Debride haemorrhagic blisters unless they are likely to rupture during transport to definitive care

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Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite: 2019 Update

Scott E. McIntosh, MD, MPH [1]; Luanne Freer, MD [2,3]; Colin K. Grissom, MD [4]; Paul S. Auerbach, MD, MS [5]; George W. Rodway, PhD, APRN [6]; Amalia Cochran, MD [7]; Gordon G. Giesbrecht, MD [8]; Marion McDevitt, DO, MPH [9]; Christopher H. Imray, MD [10]; Eric L. Johnson, MD [11]; Prativa Pandey, MD [12]; Jennifer Dow, MD [13]; Peter H. Hackett, MD [14,15]

Table 1. Summary of field treatment of frostbite (>2 h from definitive care)

Treat hypothermia or serious trauma
1. Remove jewelry or other extraneous material from the body part.
2. Rapidly rewarm in water heated and maintained betwee 37 and 39°C (98.6 and 102.2°F) until area becomes sof and pliable to the touch (approximately 30 min); allow spontaneous or passive thawing if rapid rewarming is n possible.
3. Ibuprofen (12 mg·kg^{-1} per day divided twice daily) if available.
4. Pain medication (eg, opiate) as needed.
5. Air dry (ie, do not rub at any point).
6. Protect from refreezing and direct trauma.
7. Apply topical aloe vera cream or gel if available.
8. Dry, bulky dressings.
9. Elevate the affected body part if possible.
10. Systemic hydration.
11. Avoid ambulation on thawed lower extremity (unless only distal toes are affected).

Table 2. Summary of initial hospital management of frostbite

1. Treat hypothermia or serious trauma.
2. Rapidly rewarm in water heated and maintained between 37 and 39°C (98.6 and 102.2°F) until area becomes soft and pliable to the touch (approximately 30 min).
3. Ibuprofen (12 mg·kg^{-1} per day divided twice daily).
4. Pain medication (eg, opiate) as needed.
5. Tetanus prophylaxis.
6. Air dry (ie, do not rub at any point).
7. Debridement: selectively drain (eg, by needle aspiration) clear blisters and leave hemorrhagic blisters intact.
8. Topical aloe vera every 6 h with dressing changes.
9. Dry, bulky dressings.
10. Elevate the affected body part if possible.
11. Systemic hydration.
12. Thrombolytic therapy: consider for deep frostbite at the distal interphalangeal joint or proximal if less than 24 h after thawing; use angiography for prethrombolytic intervention and monitoring of progress. Consider intravenous thrombolysis if angiography is not available.
13. Iloprost therapy: consider for deep frostbite to or proximal to the proximal interphalangeal joint, within 48 h after injury, especially if angiography is not available or with contraindications to thrombolysis.
14. Clinical examination (plus angiography or technetium-99 bone scan if necessary) to assist determination of surgical margins. Evaluation by an experienced surgeon for possible intervention.

Frostbite impact on the military

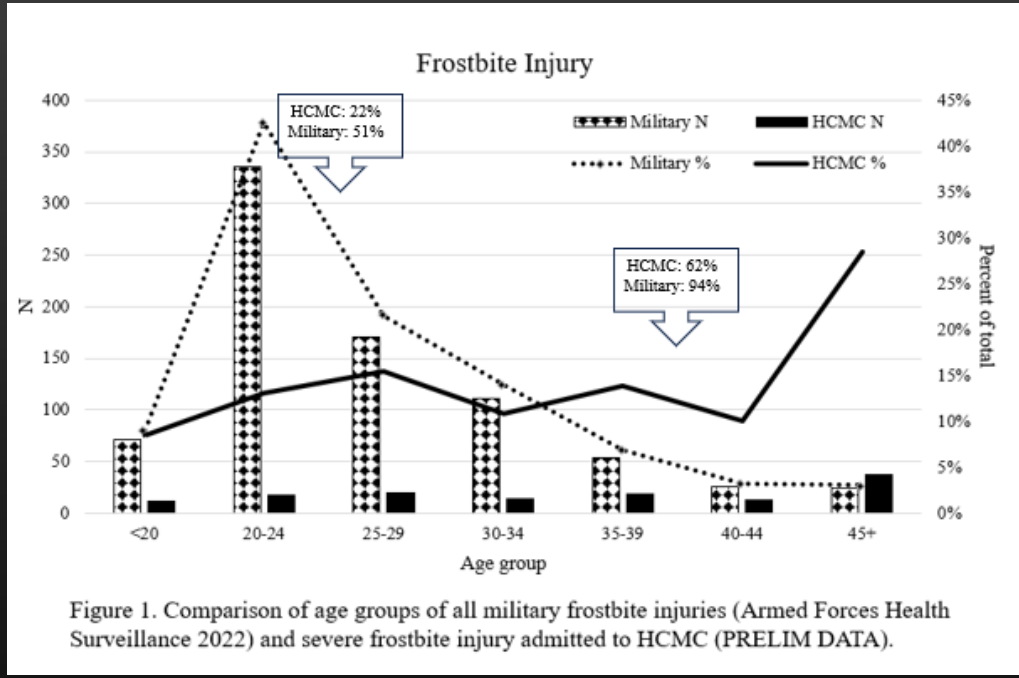
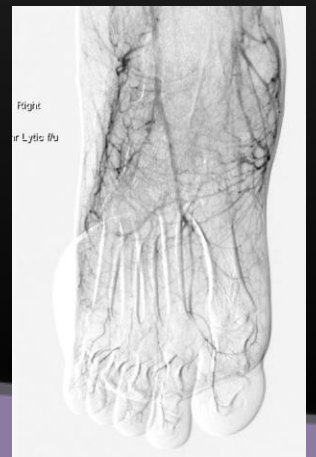
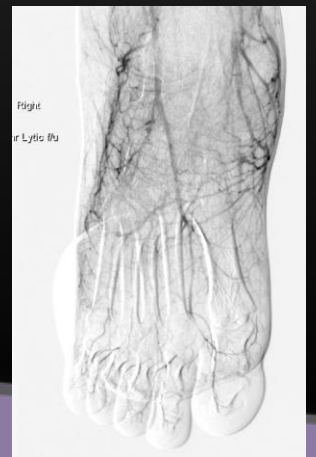


Figure 1. Comparison of age groups of all military frostbite injuries (Armed Forces Health Surveillance 2022) and severe frostbite injury admitted to HCMC (PRELIM DATA).

- Armed Forces Health Surveillance Division. Cold Weather Injuries Among the Active and Reserve Components of the U.S. Armed Forces, July 2018-June 2023. MSMR. 2023 Nov 20;30(11):2-11. PMID: 38051632.
- Armed Forces Health Surveillance Division. Update: Cold Weather Injuries, Active and Reserve Components, U.S. Armed Forces, July 2015-June 2020. MSMR. 2020 Nov;27(11):15-24.
- Endorf FW, Nygaard RM. Social Determinants of Poor Outcomes Following Frostbite Injury: A Study of the National Inpatient Sample. J Burn Care Res. 2021 Nov 24;42(6):1261-1265.

	After rewarming	Imaging	Progression	Outcome
Case 1				
Case 2				
Case 3				

	After rewarming	Imaging	Progression	Outcome
Case 1				
Case 2				
Case 3				

	After rewarming	Imaging	Progression	Outcome
Case 1				
Case 2				
Case 3				

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Supportive Cares

- Pharmacy
  - Ibuprofen - 600 mg TID with meals
  - Gabapentin - 300 mg TID
  - Lovenox therapeutic dose x 7 days post tPA
    - prophylactic dose while inpatient
    - Aspirin 81mg as outpatient
- PT/OT
  - Provide adaptive equipment
  - Active ROM and blocking exercises
- Wound cares (daily)
  - Baby soap and water
  - Topical aloe & Bacitracin
  - Conforming gauze & elastic flex netting
- Surgery
  - Debride and remove serous blisters
  - Small blisters (around ~1cm or less) without significant fluid, may be left intact regardless of their nature
  - Leave hemorrhagic blisters intact - debride after 72 hours