PEDIATRIC CRITICAL CARE GUIDELINES

Alberta Children's Hospital

Alberta Health Services

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

CONTACT

The adult version of this document was originally prepared by Emergency Departments in the Calgary Zone in partnership with the Calgary Zone Departments of Critical Care Medicine, Internal Medicine, and Surgery.

Adult Committee Members:

Alexis Mageau	Clinical Nurse Specialist	Emergency Calgary
Dan Cashen	Clinical Nurse Specialist	Critical Care Calgary
Phillipe Boilard	Clinical Pharmacist	Emergency Calgary
Dr. Ian Walker	Acting Deputy Department Head	Emergency Calgary
Dr. Peter Jamieson	Medical Director Associate Zone Medical Director	Foothills Medical Centre Calgary
Dr. Duncan Nickerson	Medical Director, Burn Program	Plastic Surgery Calgary
Dr. Tom Stelfox	Department Head	Critical Care Calgary

For more information on the adult protocol, please contact:

Alexis Mageau
Clinical Nurse Specialist
Emergency – Calgary Zone
Alexis.Mageau@albertahealthservices.ca

Dr. Ian Walker
Acting Deputy Department Head
Emergency – Calgary Zone
Ian.Walker@albertahealthservices.ca

This version that also covers pediatric cases was developed by Dr Simon J Parsons, Pediatric Intensivist, ACH Simon.Parsons@ahs.ca in conjunction with Dr Frankie Fraulin (Plastic Surgery, ACH) and with input from

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

Hematology, ED and IR. The pediatric component is significantly different from the adult protocol in that it is more aggressive. TPA is recommended for lower grade frostbite lesions and hyperbaric oxygen is used.

INTRODUCTION

Although literature on this topic pertaining to children is sparse, similar principles and therapeutic options should be considered for children with severe frostbite after consultation with Pediatric Plastic Surgery, Hematology and Intensive Care.

The purpose of the original adult document was to provide direction in the provision of care primarily to adult patients with severe frostbite. On review of the literature and local limited ACH experience, this pediatric document is significantly different from the adult version, with a more aggressive approach in terms of use of Alteplase and the additional of hyperbaric oxygen therapy (HBO).

In all pediatric cases, Plastic Surgery, Hematology and PICU should be contacted immediately. Iloprost and Alteplase (TPA) infusion therapy should only be commenced in the PICU with appropriate non-invasive monitoring, as pediatric experience is very limited and severe hypotension and bleeding may occur.

Note that the use of an arterial line for hemodynamic monitoring is contraindicated in the presence of distal limb frostbite.

ASSESSMENT AND INITIAL CARE

Rewarming

All patients presenting with frostbite should undergo rapid rewarming. The ideal temperature for rewarming bath is 37-39 degrees Celsius. Care should be taken not to inadvertently cause compounded injury with thermal burns.

Warmed 0.9% NaCl or tap water can be used in the rewarming bath. Add **chlorhexidine gluconate 2%/ isopropyl alcohol 4% solution (30 mL per liter of fluid**). The chlorhexidine gluconate 2%/ isopropyl alcohol 4% can be ordered on Connect Care. Note this solution is not standard. The PICU carries only 2%/70% (pink solution) or 2% alcohol free (almost clear solution).

chlorhexidine, aqueous-isopropyl alcohol liquid topical 2%-4% topical

The temperature of the water may be measured using a sterile temperature probe (that is usually used to monitor core temperature). Tape the probe to the inside of the basin/tub and connect to CRM in the PICU.

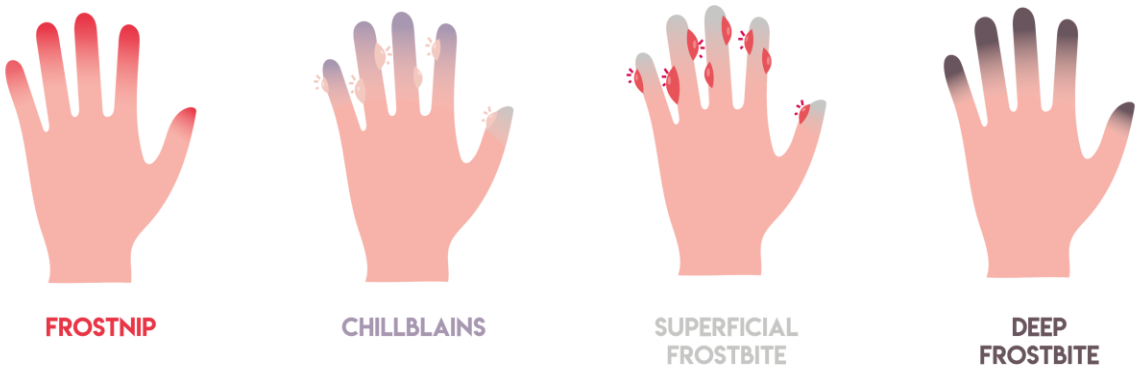
Typically, the rewarming will take approximately 30–60 minutes. Following rewarming skin should be allowed to air dry and friction drying should be avoided.

Grading of Frostbite

Note that the Staging seen below is different from Grading. Grading refers to the degree of deep frostbite.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

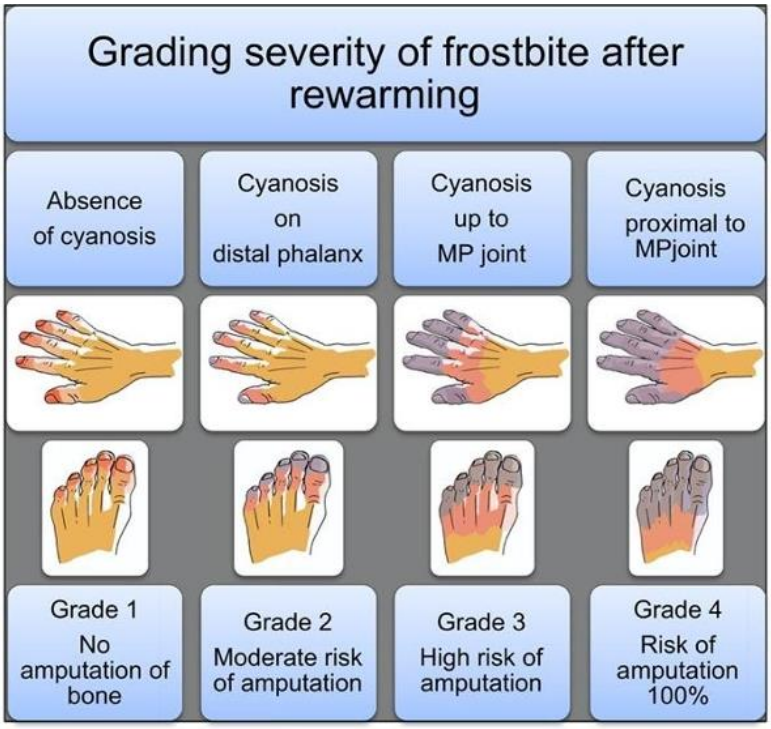
Staging



Grading for Deep Frostbite

Care should be guided by the frostbite grade, which should be assessed after rewarming. The frostbite injury may evolve in the first 24 hours, but initial treatment decisions should be made based on the initial assessment**. If a patient initially thought to have a Grade 1 frostbite subsequently proves to have a Grade 2 or Grade 3 frostbite, appropriate therapy can be initiated at that time.**

Grading should be performed by the MRP utilizing the scale developed by Cauchy et al (2016):



Facial frostbite injuries (e.g., ears, cheeks and nose) should be assessed also and should also be considered for infusion therapy, although experience with infusion therapy in such cases is limited.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

Management of Associated Hypothermia and Other Injuries

Core temperature should be monitored for all patients that are suspected to have significant hypothermia. Priority should be given to treatment of significant hypothermia or other life or limb threatening injuries.

Wound Care

All frostbite patients should receive general wound care and dressings, elevation of the affected extremity whenever possible, appropriate analgesia (consider consulting Acute Pain Service), including regular ibuprofen 10 mg/kg PO (MAX 600 mg) every 8 hours (for anti-platelet, anti-inflammatory and anti-prostaglandin effect) assuming there are no contra- indications, and tetanus toxoid as required. Early referral to ACH physiotherapist wound care team is required.

NOTE: Ibuprofen should not be utilized if Alteplase use is anticipated.

Involvement of the Plastic Surgery, Hematology and Interventional Radiology

Any patients being admitted to the hospital for management of their frostbite should be assessed by the Plastic Surgery service as soon as possible (*this may be the morning after an overnight admission, but telephone advice will be available after hours, and a decision to treat must be made immediately after rewarming*).

The decision to treat with vasoactive medications (Iloprost) or thrombolytics (Alteplase) and hyperbaric oxygen (HBO) should be a joint decision between Plastic Surgery, PICU, Hematology and Interventional Radiology. Plastic surgery will advise regarding ongoing would care strategies e.g., blister management.

Connect Care Order Sets

A frostbite order set do not yet exist in Connect Care currently. However individual order sets for IV Iloprost, Alteplase and heparin/enoxaparin do exist, but note that the recommended dosing options may not be correct for this specific indication.

SPECIFIC TREATMENT

There is a significant chance of digit loss requiring amputation in any grade of frostbite > Grade 1. In the Calgary Zone adult protocol Iloprost is used for any injury > Grade 1, but Alteplase is only recommended for Grade 4 injury. **At the ACH, we would consider Alteplase in addition to Iloprost for lower grades of injury (2-3) also.**

Newer case series also suggest that direct intra-arterial Alteplase may result in higher rates of digital salvage than systemic Alteplase, thus Interventional radiology should be consulted for frostbite grades >2.

Also, the adult protocol does not include HBO. There is reasonable evidence that HBO may have additional benefit when added to Iloprost and Alteplase as an early treatment option, and as a late treatment option alone.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

Grade 1

- Daily wound care as prescribed

Grade 2

- **Iloprost infusion daily for 5 days if within 72 hours of rewarming**
- **Strongly consider systemic Alteplase**
- **Strongly consider HBO**

NOTE: Hypotension caused by Iloprost should NOT be managed with fluid boluses or vasopressor medication, but by down titration of the dose. Fluid boluses and vasopressors may aggravate frostbite injury.

Grade 3-4

- **Iloprost as per Grade 2**
- **Intra-arterial regional Alteplase** should be first considered urgently, with consultation of Interventional Radiology and PICU. Note that published series currently indicate a higher digit salvage rate with intra-arterial TPA versus systemic TPA but RCTs are lacking.
- **If IA Alteplase cannot be administered (e.g., non-limb frostbite such as nose and ear, multiple limbs affected, or unexpected delay to main treatment center or IR is not available:**
- **Alteplase infusion for 6 hours on day 1 if within 24 hours of rewarming**
    - To start after the first hour of Iloprost infusion and run simultaneously with Iloprost infusion
    - Note the adult protocol includes an initial 0.15 mg/kg Alteplase bolus that can be considered in older children
- **Heparin infusion (without an initial bolus) to be administered concomitantly with alteplase and continued for at least 72 hrs. Alternatively S/C enoxaparin should be prescribed if surgical intervention is unlikely to be required urgently. Remember DVT prophylaxis is eligible children.**
- **HBO started as soon as possible, daily for up to 2 weeks according to response.**

Iloprost

Points of Emphasis

- Iloprost is a synthetic analogue of prostacyclin (prostaglandin I_2)
- The administration of Iloprost is approved by Health Canada for frostbite.
- Iloprost is a Special Access Program (SAP) medication requiring SAP documentation (Health Canada's special access programs: Request a drug - Canada.ca). Order the first dose on Connect Care and Pharmacy will provide SAP documentation to be completed with every other infusion.
- Iloprost is administered by intravenous (IV) infusion only in the context of frostbite. Inhaled forms are used in pulmonary hypertension and ARDS.
- Iloprost is a high-alert medication and requires an independent double check. Refer to the high-alert medication policy for more information.
- In patients presenting later than 5 days, still consider Iloprost
- Consider extending infusion duration past 6 hrs if clinical deterioration occurs on stopping the daily infusion
- It can be run continuously for 5+ days.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

Contraindications to the Administration of Iloprost

Absolute contraindications include patients with the following:

- Known hypersensitivity to Iloprost or excipients

Relative contraindications include:

- Pregnancy, lactation.
- Systolic blood pressure less than 85 mmHg *(or equivalent age-appropriate 5th percentile systolic BP in children).*

Exercise caution in patient populations with:

- History of cerebrovascular event within the last 3 months;
- Increased risk of bleeding;
- Hepatic impairment;
- Myocardial infarction within the last 6 months;
- Acute or chronic congestive heart failure;
- Severe coronary heart disease or unstable angina, and/or;
- Severe arrhythmias.

Preparation

Iloprost must be stored and prepared per the AHS provincial parenteral manual instructions. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Key Points:

- Store at room temperature;
- Dilute 50mcg in Dextrose 5% (D5W) 250 ml bag for a final concentration of 0.2mcg/ml;
- Maximum dose = 50 mcg/daily;
- The MRHP or designate will be readily available for at least 10 minutes following the initiation of any infusion or dosage increase for patients in which significant hypotension has occurred with earlier infusions, or during the initial infusion.

Administration

Use the Baxter Critical Care Library: option iloprost mcg/hr OR nanogram/kg/min. Iloprost is administered using the following steps:

- Start the intravenous solution at 2 mcg/hour, then increase dose by 2 mcg/hour every 30 minutes as tolerated, up to:
  - a MAX rate of 6 mcg/hour for patients 40 to 50 kg
  - a MAX rate of 8 mcg/hour for patients 51 to 74 kg or
  - a MAX rate of 10 mcg/hour for patients 75 kg or more
- Continue infusion for 6 hours daily regardless of the rate.
- **Note**: There may be extra iloprost in the infusion bag and IV tubing. Please discard after the 6 hour infusion is complete
- Repeat infusion daily for 5 days
- If tolerated well on day 1 and 2, infusion may be started at the maximum rate on days 3, 4, and 5.
  - For patients 40 -50 kg and 51 – 74 kg: administer over 6 hours
  - For patients greater than 75 kg: infuse at a maximum rate of 10 mcg/hr for 6 hours or until bag is depleted (likely within 5 hrs). Maximum dose is 50 mcg/daily.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

PEDIATRIC DOSING

The above adult infusion rates equate to 0.11-0.16 mcg/kg/hour, average 0.13 mcg/kg/hour, max 10 mcg/hour, max total daily dose 50 mcg. The equivalent starting dose in 1/5-1/3 of the above dose, titrated up every 30 min.

So < 40 kg

- ***Start at 0.05 mcg/kg/hour (0.83 nanograms/kg/min)***
- ***Titrate up every 30 min by additional 0.05 mcg/kg/hour, if systolic BP ≥5th percentile 70 mmHg + 2 x age in years)***
- ***Max dose 0.15 mcg/kg/hour (2.5 nanograms/kg/min, MAX 10 mcg/hour)***
- ***Continue for total 6 hours***
- ***Repeat daily for 5 days – NOTE the infusion duration can be extended***
- ***If infusions day 1 and 2 tolerated well, start day 3 at max rate.***
- ***If hypotension occurs, do not support with vasopressors or fluid boluses (unless hypovolemia is suspected), simply hold Iloprost at highest tolerated dose.***

During the administration of Iloprost monitor blood pressure and heart rate every 15 minutes for two hours, then decrease frequency to every 30 minutes.
Following the initiation of the Iloprost infusion, monitor for the following potential side effects:

- headaches
- tachycardia
- hypotension
- palpitations
- nausea
- vomiting
- facial flushing

If any of the above side effects are develop, decrease the infusion rate by 2 mcg/hour *(or decrease by an amount equivalent to the initial starting dose in children)* and re-assess 30 minutes later. Notify MRHP if side effects persist.

Alteplase

Points of Emphasis

- Indicated for grade 2-4 frostbite injury if less than 24 hours since rewarming.
- Administer alteplase dose within first hour of Iloprost infusion.
- Alteplase must be given as soon as possible, within 24 hours of rewarming. Consider full dose, or lose dose therapy as a safer alternative, if there is a real risk of tissue loss or amputation and still within 24-48 hrs of rewarming.
- Only a single 6 hr infusion is recommended. Longer infusions are associated with an increased risk of bleeding.

Contraindications to the Administration of Alteplase

Absolute contraindications include patients with the following:

- history of any intracranial hemorrhage

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

- presence of a cerebral vascular malformation
- known primary or metastatic intracranial malignancy
- symptoms or signs suggestive of an aortic dissection
- a bleeding diathesis or active bleeding with the exception of menses
- significant closed-head or facial trauma within the preceding 3 months
- intracranial or intraspinal surgery within 2 months
- uncontrolled hypertension at presentation (unresponsive to emergency treatment).

Relative contraindications include:

- history of chronic, severe, poorly controlled hypertension
- uncontrolled hypertension at presentation (systolic blood pressure greater than 180 mmHg and/or diastolic blood pressure greater than 110 mmHg in adults)
- history of ischemic stroke more than 3 month previously
- dementia
- traumatic or prolonged (greater than 10 minutes of Chest Compressions (CPR)
- any known intracranial disease that is not an absolute contraindication
- major surgery within the preceding 3 weeks
- recent internal bleeding
- recent gastrointestinal or genitourinary bleeding (within 10 days)
- non compressible vascular punctures
- pregnancy
- current use of anticoagulants such as warfarin, LMWH and Direct Oral Anticoagulants.

Exercise Caution: Patients with history of ischemic stroke within the preceding 3 months, consult stroke service.

Preparation

Alteplase must be stored and prepared per the AHS provincial parenteral manual instructions. It is essential to follow directions carefully and to adhere to strict aseptic procedures during preparation.

Key Points:

- Store unopened vials at room temperature or in the refrigerator and protect from light
- Administer alteplase bolus dose followed by an intermittent infusion
- Dilute alteplase solution to a concentration of 1mg/ml - no further dilution is required
- Alteplase in this patient population requires an Independent Double Check

Dosing (adult):

- Bolus: give 0.15 mg/kg intravenous over 15 minutes
- Infusion: give 0.15 mg/kg/hr for a total of six (6) hours
- Total MAX dose (including bolus = 100 mg)

PEDIATRIC DOSING

As above for adults BUT WITHOUT initial bolus dose.

- ***Infusion: give 0.15 mg/kg/hr for a total of six (6) hours***
- ***Total MAX dose (including bolus = 100 mg)***

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

- ***Doses as low as 0.01-0.06 mg/kg/hr have also been effective in children for large vessel thromboses of other causes***

Administration

Use the Baxter Critical Care Library: option Alteplase infusion mg/kg/hour.

Note: There may be extra alteplase in the infusion bottle and tubing. Please discard after the 6-hour infusion is complete.

During the administration of alteplase monitor blood pressure and heart rate every 15 minutes for two hours, then decrease frequency to every 30 minutes. Monitor neurological vital signs at baseline and every 30 minutes for the 6-hour infusion, then every 30 minutes for 3 hours post infusion.

Following the initiation of the alteplase infusion, monitor for the following potential side effects:

- headaches
- tachycardia
- hypotension
- bleeding

If any of the above side effects are present, notify the MRHP immediately.

Intra-arterial Alteplase

Interventional radiology will determine the intra-arterial dosing and duration.

Heparin

Start heparin within 1 hour of starting alteplase dose. Continue for 72 hrs. For children use heparin infusion dosing recommendations in Arterial Occlusion guideline (https://pccg.cornerstonedigital.ca/wp-content/uploads/2020/12/tms-picuc-physician-arterial-occlusion-in-children.pdf)

PEDIATRIC DOSING: Use Connect Care heparin infusion order set. Consult Hematology for all children. Enoxaparin is an alternative to consider.

Hyperbaric Oxygen Therapy (HBO)

HBO Monday-Friday (7am-6pm) call FMC HBO 403 9446645 and ask to speak to physician on call. After hours and on weekends call the Hyperbaric Physician on call at FMC via ROCA > FMC > Other > Hyperbaric.

The hyperbaric chamber has a very limited ability and room to care for unstable children.

In all cases of ≥ Garde 2, consider urgent HBO daily for up to 14 days, starting after the completion of the TPA infusion (likely day 2).

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

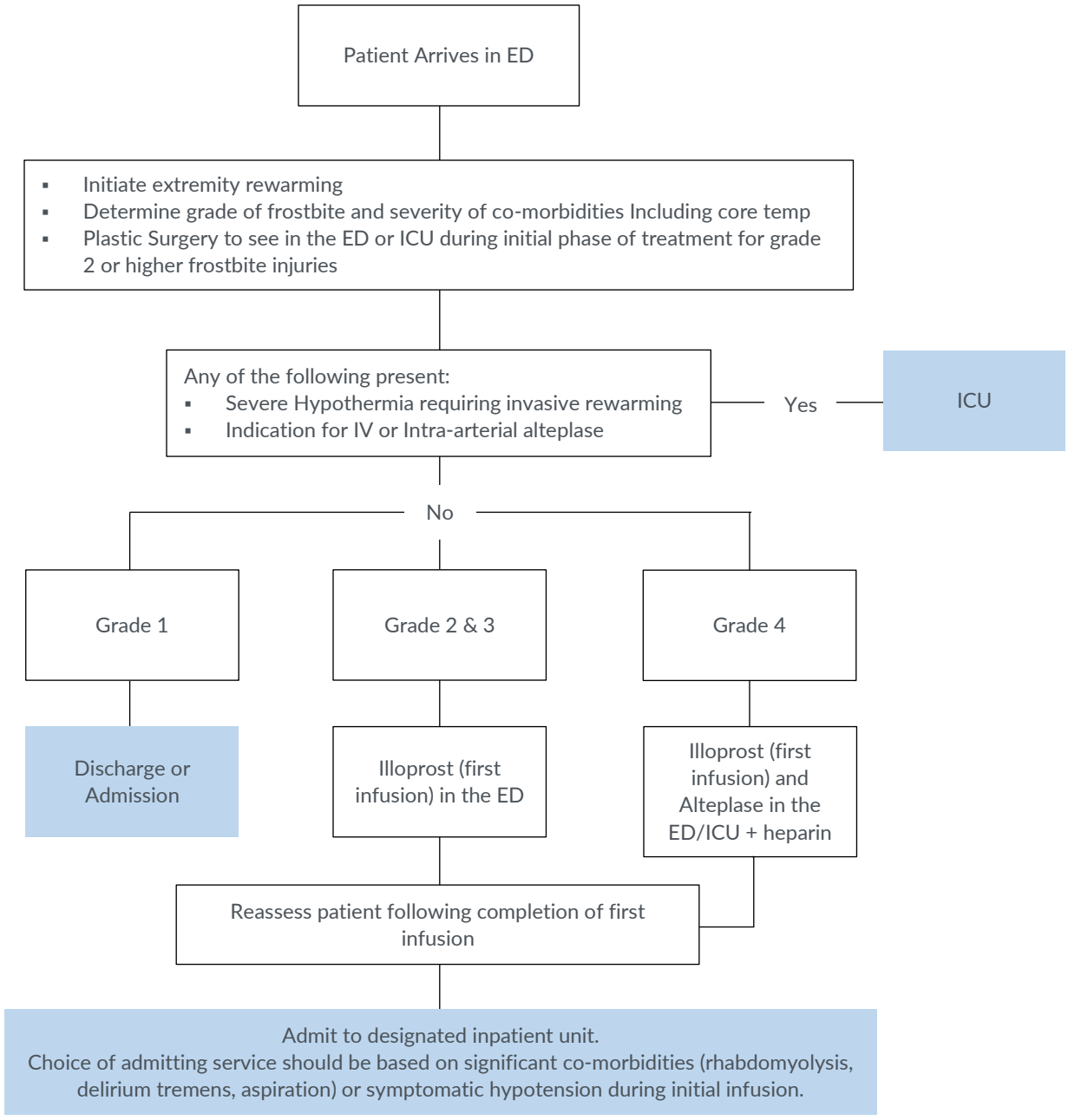
There are significant limitations to the capability of the Calgary HBO chamber. The treatments are 2 hours in duration during which time the child must be alone in the chamber without IV therapy running.

Thus, assess to this therapy may be limited by the need for ongoing Iloprost and analgesic infusions, clinical instability, age, and level of patient cooperativeness.

The Edmonton and Vancouver HBO chambers can cater for higher levels of acuity.

HBO can be considered as a stand-alone therapy if the patient presents > 24 hours after rewarming.

Adult Patient Disposition Algorithm



CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

Pediatric Disposition

At ACH, all cases requiring Iloprost with or without Alteplase **will be admitted to the PICU** as soon as possible for the initiation of the infusions. Once the target dose of Iloprost is tolerated for 2 infusions, subsequent infusions can be undertaken outside the PICU. TPA administration should occur in the PICU.

REFERENCES

[1] Use of Thrombolytic Agents to Treat Neonatal Thrombosis in Clinical Practice. Leong R, Patel J, Nasrin S, Paes B, Chan AKC, Petropoulos J, Bhatt MD, Thrombosis, Hemostasis in Newborns (THiN) Group. Blood Coagul Fibrinolysis 2022 Jun; 1;33(4): 193-200.

[2] Infusion Techniques for Peripheral Arterial Thrombolysis. Broderick C, Patel JV. Cochrane Database Syst Rev. 2023 Nov 17; 11(11).

[3] Clinical Experience with Alteplase in the Management of Intracardiac and Major Cardiac Vessels Thrombosis in Pediatrics: a Case Series. Al-Jazairi AS, Al-Gain RA, Bulbul ZR, Cherfan AJ. Ann Saudi Med. 2020 May-Jun; 30(3): 227-32.

[4] Thrombolysis in Children: A Case Report and Review of the Literature. Woods GM, Kim DW, Paden ML, Viamonte HK. Font Pediatrics. 2022 Jan 25; 9:814033.

[5] Bleeding Complications in patients with Severe Frostbite Injury. Murphy J, Endorf FW Winters MK, Rogers , Wlater E, Neumann N, Weber L, Lacey AM, Punjabi G, Nygaard Rm. J Burn Care Res. 2022 Dec 9: irac180.

[6] Remote Delivery of Thrombolytics Prior to Transfer to a Regional Burn Center for Tissue Salvage in Frostbite: A single-center Experience of 199 Patients. Carmichael H, Michael S, Smith TM, Duffy PS, Wiktor AJ, Lamber Wagner A. Journal of Burn Care & Research. 2022 Jan 5'43(1):54-60.

[7] Use of Intra-arterial Thrombolytic Therapy for Acute Treatment of Frostbite in 62 Patients with Review of Thrombolytic Therapy in Frostbite. Gonzaga T, Jenavzadeh K, Anderson CP, Mohr WJ, Endorf FW, Ahrenholz DH. Jounral of Burn Care & Research. 2016 Jul-Aug37(4):e323-34.

[8] Thrombolytic Salvage of the Frostbitten Upper Extremity: A Systematic Review. Drinane J, Heiman AJ, Ricci JA, Patel A. Hand (N Y). 2022 May; 17(3):397-404.

[9] Protocoled Thrombolytic Therapy for Frostbite Improves Phalangeal Salvage Rates. Paine RE, Turner EN, Kloda D, Falank C, Chung B, Carter DW. Burns Trauma. 2020 Apr 10;8:tkaa008.

[10] Time Matters in Severe Frostbite: Assessment of Limb/Digit Salvage on the Individual Patient Level. Nygaard RM, Lacey AM, Lemere A, Dole M, Gayken JR, Lambert Wagner AL, Fey RM. Journal of Burn Care & Research. 2017 Jan/Feb;38(1):53-59.

[11] Thrombolytic Salvage of the Frostbitten Upper Extremity: A Systematic Review. Drinane J, Heiman AJ, Ricci JA, Patel A. Hand (N Y). 2022 May;17(3):397-404.

[12] Thrombolytic Use n Management of Frostbite Injuries: Eight Year Retrospective Review at a Single Institution. Heard J, Shamrock A, Galet C, Pape KO, Laroia S, Wibbenmeyer L. Journal of Burn Care & Research. 2020 May 2;41(3):722-726.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

[13] Effectiveness of Intravenous Prostaglandin to Reduce Digital Amputations from Frostbite: an Observational Study. Crooks S, Shaw BH, Andruchow JE, Lee CH, Wlkaer I. CJEM. 2022 Sep;24(6):922-629.

[14] Management of Severe Frostbite with iloprost, alteplase and heparin: a Yukon case series. Poole A, Gauthier J, MacLennan M. CMAJ Open. 2021 May 21;9(2):E585-E591.

[15] Case Report: Severe Frostbite in Exteme Altitude Climbers – The Kathnamdu Iloprost Experience. Pandey P, Vadlamudi R, Pradhan R, Pandey KR, Kumar A, Hackett P. Wilderness Environ Med. 2018 Sep;29(3):366-374.

[16] A Controlled Trial of a Prostacyclin and rt-PA in the Treatment of Severe Frostbite. Cauchy E, Cheguillaume B, Chetaille E. The New England Journal of Medicine. 2011 Jan 13; 364:189-190.

[17] The Evolution of the Helsinki Frostbite Management Protocol. Lindofrd A, Valtonen J, Hult M, Kavola H, Lappalainen K, Lassila R, Aho P, Vuola J. Burns: Journal of the International Society for Burn Injuries. 2017 Nov; 43(7):1455-1463.

[18] Deep Frostbite Treated With Hyperbaric Oxygen and Thrombolytic Therapies. Higdon B, Youngman L, Regehr M, Chiou A. Wounds: a Compendium of Clinical Research and Practice. 2015 Aug; 27(8):215-23.

[19] A New Proposal for Management of Severe Frostbite in the Austere Environment. Cauchy E, Davis CB, Pasquier M, Meyer EF, Hackett PH. Wilderness & Environmental Medicine. 2016 Mar; 27(1):92-9.

[20] Hyperbaric Oxygen Therapy with Iloprost Improves Digit Salvage in Severe Frostbite Compared to Iloprost Alone. Magnan MA, Gayet-Ageron A, Louge P, Champly F, Joffre T, Lovis C, Pignel R. Medicina (Kaunas). 2021 Nov 22;57(11):1284.

[21] A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. Cauchy E, Cheguillaume B, Chetaille E. N Engl J Med 2011;364:189-90.

[22] Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. Cauchy E, Chetaille E, Marchand V, et al. Wilderness Environ Med 2001;12:248-55.

[23] Treatment of frostbite with iloprost. Groechenig E. Lancet 1994; 344:1152-3.

[24] Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite. McIntosh SE, Hamonko M, Freer L, et al. Wilderness Environ Med 2011;22:156-66.

[25] Treatment of Severe Frostbite with Iloprost in Northern Canada. Poole, A., Gauthier, J. CMAJ 188(17-18), 2016. 1255-1258.

[26] An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. Twomey JA, Peltier GL, Zera RT. J Trauma 2005;59:1350-4.

[27] Hyperbaric Oxygen Therapy with Iloprost Improves Digit Salvage in Severe Frostbite Compared to Iloprost Alone. Magnan MA, Gayet-Ageron A, Louge P, Champly F, Joffre T, Lovis C, Pignel R.Medicina (Kaunas). 2021 Nov 22;57(11):1284.

[28] A Photographic Case of Frostbite Treated with Delayed Hyperbaric Oxygen Therapy. Davis A, Sinopoli B, Mann N, Stenbit AE. High Alt Med Biol. 2022 Jun;23(2):194-197.

CARE OF THE ADULT AND CHILD WITH SEVERE FROSTBITE

[29] Diagnosis and Treatment of Frostbite. Sheridan RL, Goverman JM, Walker TG. N Engl J Med. 2022 Jun 9;386(23):2213-2220.

[30] Thrombolytic Salvage of the Frostbitten Upper Extremity: A Systematic Review. Drinane J, Heiman AJ, Ricci JA, Patel A.Hand (N Y). 2022 May;17(3):397-404.

[31] Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. Poole A, Gauthier J, MacLennan M. CMAJ Open. 2021 May 21;9(2):E585-E591

[32] Protocoled thrombolytic therapy for frostbite improves phalangeal salvage rates. Paine RE, Turner EN, Kloda D, Falank C, Chung B, Carter DW. Burns Trauma. 2020 Apr 10;8.

[33] What Interventional Radiologists Need to Know About Managing Severe Frostbite: A Meta-Analysis of Thrombolytic Therapy. Lee J, Higgins MCSS.AJR Am J Roentgenol. 2020 Apr;214(4):930-937.

[34] Thrombolytic Use in Management of Frostbite Injuries: Eight Year Retrospective Review at a Single Institution. Heard J, Shamrock A, Galet C, Pape KO, Laroia S, Wibbenmeyer L.J Burn Care Res. 2020 May 2;41(3):722-726.

[35] Diagnosis and Treatment of Frostbite. Sheridan RL, Goverman JM, Walker TG.N Engl J Med. 2022 Jun 9;386(23):2213-2220.

[36] Low dose tissue plasminogen activator treatment for vascular thrombosis following cardiac catheterization in children: a single center experience. Bratincsák A, Moore JW, El-Said HG. Catheter Cardiovasc Interv. 2013 Nov 1;82(5):782-5.