Management of Non-Chemo Drug Extravasation

Some non-chemo vesicant drugs may be especially likely to harm soft tissue with infiltration or extravasation.[21,22] **They can be classified as**:[16,17,21,22,25]

- **Hyperosmolar meds** (e.g., hypertonic saline, parenteral nutrition, sodium bicarbonate) cause osmotic shifts leading to inflammation and cell death.
  - Common preventive strategies: Infuse through a central line. In particular, ≥600 mOsm/L may not be as well tolerated by peripheral veins.[21,22] (For reference, the osmolarity of 0.9% sodium chloride is 308 mOsm/L and for 3% saline it's 1,026 mOsm/L.)
- **Drugs with very high or low pH** (e.g., acyclovir, amiodarone, phenytoin, vancomycin), which damage tissue and cause vasoconstriction.
  - Common preventive strategies: Dilute medication and infuse slowly. See detailed recommendations below.
- **Vasopressors** (e.g., norepinephrine, phenylephrine, vasopressin), which cause ischemia and necrosis.
  - Common preventive strategies: Infuse through a central line, especially for longer durations and if a large peripheral vein is not available.[25]

General treatment for non-chemo extravasations includes these steps:[1-3,15,17,18,21,22,24]

- Immediately stop the infusion.
- Aspirate residual drug through the needle or catheter.
- Elevate the affected limb to minimize swelling.
- Apply a **cold** (to reduce swelling and localize the agent) **OR** a **warm** (for vasodilation and to disperse the agent) compress. Apply dry compresses for 20 minutes every 6 to 8 hours for up to 3 days.[2,22,24] The choice of **cold or warm** will depend on the offending agent.
- Administer an analgesic.

Drug treatments depend on the causative agent, and may include the following: (doses below have been cited in the literature):

- To distribute the causative agent away from the site (commonly used for hyperosmolar and pH-related extravasation injury):
  - **Hyaluronidase** (US only) 150 units/mL. Dilute to 15 units/mL with 0.9% sodium chloride. Inject 0.2 mL intradermally, into five sites around the extravasation area.[8,22] Administer within about one hour of extravasation.[18,22] Note that warm compresses may complement the action of hyaluronidase, while cold compresses may theoretically act in opposition.[21]
- To counteract local vasoconstriction (commonly used for vasopressor extravasation):
  - **Phentolamine** 5 to 10 mg, in 10 to 20 mL 0.9% sodium chloride, intradermal or subcutaneously, around the edges of the extravasation area as multiple small injections (e.g., 0.2 to 1 mL at a time [using a new needle for each injection]).[21,22] Administer as soon as possible to prevent tissue necrosis (best outcomes within 12 hours of extravasation).[22,27]
  - **Terbutaline** (US only) 1 mg in 10 mL 0.9% sodium chloride (for larger areas) or 1 mL 0.9% sodium chloride (for localized ischemia). Administer subcutaneously at the edges of the extravasation area.[22,24,25] Can repeat dose after 15 minutes.[22]
  - **Nitroglycerin** topical formulations used include patch or 2% ointment (US only), as a 1-inch strip, every 8 hours as needed.[14,21,22,24]

Silver sulfadiazine cream may help with extravasation of hyperosmolar drugs.[21] Topical or systemic steroids have not been shown to be effective and can slow healing and promote infection.[21] Severe cases may require surgical intervention.[16,17,22] **Note that treatments are often based on case reports and animal data**.

The following chart contains non-chemo drugs that have some evidence for treatment of extravasation. Warm or cold compresses are included if data supporting use of one or the other are available. Some preventive strategies are also included. Additional sources of information for treating extravasations of drugs not listed may include drug manufacturers, poison control centers, or hospital protocols (consider developing protocols, if you don't already have them).

Drug	Treatment Options	Comments
Calcium salts	• **Warm** compress • Hyaluronidase[22]	• **Mechanism**: hyperosmolarity[22] • Dilute calcium chloride to 3 mg/mL or less when administering via peripheral line.[20,28]
Contrast media	• **Cold** or **warm** compress to alleviate symptoms[22] • Hyaluronidase (data are conflicting)[22]	• **Mechanism**: hyperosmolarity[3,6] • Tissue damage is most likely with ionic agents.[3,6,7]
Dextrose (≥10%)	• Hyaluronidase[8]	• **Mechanism**: hyperosmolarity[8]
Mannitol	• **Warm** compress[22] • Hyaluronidase[9,22]	• **Mechanism**: hyperosmolarity[9,21]
Methylene blue	• Topical nitroglycerin[22] • Phentolamine[22]	• **Mechanism**: vasocontriction[22]
Nafcillin (US only)	• Hyaluronidase[10]	• **Mechanism**: not clear; possibly hyperosmolarity[22]
Parenteral nutrition	• **Warm** compress[22] • Hyaluronidase[1] • Topical nitroglycerin[1,22]	• **Mechanism**: hyperosmolarity[1] • Formulations with up to 900 mOsm/L are considered safe for peripheral administration.[23]
Phenytoin	• **Warm** compress[11,22] • Hyaluronidase[12] • Topical nitroglycerin[11]	• **Mechanism**: high pH[a,11] (vehicle composition and formation of precipitates may also contribute) • Extravasation may result in "purple glove syndrome."[11]
Potassium salts	• Hyaluronidase[22]	• **Mechanism**: hyperosmolarity[22] • Adult recommended infusion rate is 10 mEq/hour.[20]

Drug	Treatment Options	Comments
		• Concentration limits for peripheral administration may vary by institution. Most allow 0.1 mEq/mL to be infused peripherally, and some may allow 0.2 mEq/mL to be infused via peripheral line.[20]
Promethazine	• No proven treatment.[4] Sympathetic blockade (i.e., nerve block) and systemic heparin therapy have been used to manage inadvertent intra-arterial administration and extravasation of promethazine based on animal data.[4,19,22]	• **Mechanism**: low pH,[a] chemical irritant[19] • Suggested preventive strategies include:[5] o Dilute doses in 0.9% sodium chloride to allow for slower administration. o Start with smaller doses such as 6.25 to 12.5 mg. o Infuse doses through a large vein over 10 to 15 minutes. • ISMP recommends removing promethazine from formulary and all areas of the hospital.[29]
Saline (3%)	• Hyaluronidase[22]	• **Mechanism**: hyperosmolarity[22]
Vasopressors • Dobutamine • Dopamine • Epinephrine • Norepinephrine • Phenylephrine • Vasopressin	• **Warm** compress[21,22,24] • Phentolamine[13] • Terbutaline[24] • Topical nitroglycerin[14,22,24]	• **Mechanism**: vasoconstriction, low pH[a,13,21,22] • Infusing pressors through central lines is usually recommended, but some data suggest the risk of extravasation injuries from infusing vasopressors through peripheral lines may be lower than thought.[26] • Hyaluronidase or cold compresses can extend/worsen vasoconstriction.[21c] • Topical nitroglycerin is preferred over phentolamine for extravasation due to vasopressin.[24]

a. Do not attempt to neutralize acidic or basic extravasations due to the potential for heat and gas formation.[21,22]

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. Am Fam Physician 2004;69:548-56. https://www.aafp.org/pubs/afp/issues/2004/0201/p548.html.]

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