ZUCKERBERG
SAN FRANCISCO GENERAL
Hospital and Trauma Center

Management of Intravenous Non-Chemotherapeutic Extravasations

Purpose:

- To provide pharmacists, nurses, and providers a reference document for the treatment of extravasation of medications.
- To inform providers of drugs and patient specific risk factors that place additional risk for infiltration.
- To reduce harm to patients and facilitate prompt treatment through pharmacist, nursing and provider education and consistent framework for treatment.

Definitions:

- Irritant: an agent that causes aching, tightness, and phlebitis with or without inflammation, but does not typically cause tissue necrosis, unless the extravasation is severe or left untreated.
- Vesicant: an agent capable of causing tissue damage when it escapes from the intended vascular pathway into surrounding tissue.
- Infiltration: inadvertent administration of non-vesicant solution or medication into the surrounding tissue.
- Extravasation: inadvertent infiltration of vesicant solution or medication into the surrounding tissue.
- Flare**:** Local, nonpainful, possibly allergic reaction often accompanied by reddening along the vein.

Table 1. Drug characteristics and mechanism of tissue injury

Non-physiologic pH	Physiologic pH is 7.35-7.45. Extreme pH exposure (i.e. pH <5 or >9) can damage venous endothelium and increase risk of vessel rupture. With extravasation, there is tissue destruction and vasoconstriction that may lead to inflammation, edema, sloughing, and ulceration. Neutralization of extreme pH should not be attempted due to the potential for exothermic or gas-producing reactions that may exacerbate the injury.
Vasoconstriction	Localized vasoconstriction attributed to extravasation reduces blood flow and may result in ischemia and necrosis. Vesicant exposed tissues are at risk from both chemically induced and mechanically induced vasoconstriction.
Osmolarity	Physiologic pH is ~ 310 mOsml/L. Both hypotonic and hypertonic solutions can cause tissue damage by forcing fluid shifts into or out of cells. Hypotonicity shifts fluid into the cell, which may result in cell rupture. Hypertonicity disrupts cellular ion transport and shifts fluid from the cells to the interstitial space, which may lead to swelling and compartment syndrome. A cycle of hypoperfusion, ischemia, and worsening edema may occur as necrosis progresses. Drug precipitation may also occur with high osmolarity vesicants like calcium and phosphate.
Cytotoxicity	Cytotoxic vesicants damage cells or tissues via direct contact.
Absorption refractory	When drugs with insolubilities or limited ability to be absorbed into the bloodstream persist in the extravasated space.

Table 2. Factors that increase risk for extravasation

Infusion-specific factors	• Duration of infusion • Catheter location in elbow, ankle, dorsum of hand, or any other flexion point • Infiltration volume	• Catheter gauge (relative to vein size) • Multiple venous access attempts proximal to venous access site • Inadequately secured catheter	• Catheter type (steel > Teflon > polyurethane) • Need for catheter readjustments • Infusion rate
Patient-specific factors	• Patient skin color (darker skin may delay detection time) • Raynaud disease • Excessive movement around venous access site • Extremes in age (elderly, neonatal)	• Hypotension or decompensated blood flow • Prior extravasation injury • Clot formation at cannulation site • Altered skin/SQ tissue integrity or venous/arterial anatomy	• Peripheral vascular disease • Unable to verbalize pain • Lymphedema • Peripheral neuropathy or altered sensory perception
Health-care specific factors	• Lack of IV access establishment or access skills	• Lack of knowledge of common vesicants	• Infiltration during overnight shift
	• Distractions or lack of monitoring for infiltration of high-risk drugs		

Table 3. Recognition of possible extravasation

Signs/symptoms (may not all be detected)	**Comments**
Pain: burning, stinging, sensation of coolness Erythema around administration site Swelling, tenderness Loss of blood return from IV device Resistance during IV bolus Leaking around catheter or implanted port needle Temperature change in tissue surrounding infusion site	Occurs within minutes of extravasation
Blistering	Around the site of infusion
Mottling/darkening of skin	Can appear patchy or as irregular colors
Hardening of skin	Hard, resistant to touch
Ulceration	Usually not evident until 1-2 weeks after injury
No capillary filling	White appearance with non-blanching skin upon pressure

Initial extravasation management:

1. Stop infusion immediately.

2. Notify the H.O. to assess extravasation site and to order antidote if warranted (see Table 4 & 5).

3. Disconnect IV line.

4. Immediately attempt to aspirate any residual drug from the catheter with a syringe and then remove catheter.
    a. EXCEPTION: Aspiration of extravasated contrast media is NOT recommended.
    b. Avoid friction or pressure to the affected area.
    c. Do NOT flush the line in attempt to dilute drug solution.

5. Provider to administer antidote if ordered.
    a. Prior to injecting the antidote, prep the skin using aseptic technique with either 10% povidone-iodine (1 min scrub time, then allow to dry) or 2% chlorhexidine gluconate (30 sec scrub time, then allow to dry). NOTE: 10% povidone-iodine is recommended if there is a break in skin integrity or friable, as a result of the extravasation injury.

6. Apply loose gauze dressing and assess extravasation area every 2 hours for the next 48 hours unless symptoms worsen. If symptoms worsen, continue to monitor, and report to provider.

7. Elevate affected limb and apply recommended thermal compress (see Table 4 & 5)
    a. Note that there is no consensus on the appropriate approach to cold or warm compresses. Apply compress for 15-20 minutes every 4 hours for 24-48 hours until inflammation/symptoms resolve.
        i. Application of a dry, cold compress to affected area results in vasoconstriction potentially limiting the spread of the drug, providing pain relief, and decreasing inflammation.
        ii. Application of a dry, warm compress to affected area results in local vasodilation and increased blood flow, which is believed to facilitate removal of the drug from the affected area.

8. Outline the extravasation area with a pen. Do not apply pressure to the area.

9. Establish another IV line immediately so that IV infusion may continue uninterrupted. Obtain access at another site not affected by the extravasation. Do not place IV distal to the extravasation site.

10. Monitor the extravasated site for further tissue injury during each nursing shift for at least the next 48 hours.

11. Submit a U.O. to document that the event occurred.

12. Primary team should consider surgical consult if there is inadequate response to antidotes, and/or if there is evidence of skin breakdown, necrosis, or concern for compartment syndrome. For extravasation injuries below the elbow, contact surgical service on hand call (rotates between plastic and ortho) and for all other sites, contact general surgery.

Table 4. Antidotes for extravasation

Antidote	Mechanism of action	Administration/Dosing
Hyaluronidase	Facilitates absorption and dispersal of drugs/fluids from extravascular space into bloodstream. Hyaluronidase dissolves hyaluronic acid, one of the binders that holds soft tissue cell layers together and forms the dermal barrier. By loosening the layers from each other, fluid can flow freely between sheets of tissue.	*For most non-chemo drugs*: Mix 0.1 ml of hyaluronidase 150 units/ml with 0.9ml NS into a syringe to make a final concentration of 15 units/ml. Inject SQ/ID a total of 1 ml (15 units/ml) as five separate injections of 0.2 ml into and around the edges of extravasation. Use a 25- or 27-gauge needle. May repeat every 30-60min up to 450 units as needed. *For D50 extravasation:* Using 150 units/ml undiluted, inject SQ/ID a total of 1 ml as five separate 0.2 ml injections into and around the edges of extravasation. Use a 25- or 27-gauge needle. May repeat every 30-60min up to 450 units as needed.
Phentolamine	Alpha -1 antagonist, vasodilator, competitively blocks effects of circulating catecholamines	Dilute 5 to 10 mg in 10 ml NS. Inject SQ/ID in small aliquots into and around the edges of the extravasation site. Use a 25- or 27-gauge needle. Administer as soon as possible but within 12 hours of extravasation. Blanching should reverse immediately. Additional doses may be required if blanching returns.
Terbutaline	Beta-2 agonist, vasodilator	Dilute 1 mg in 10 ml NS. Inject ID/SQ in 1 mL increments (up to 10 mL) into and around the edges of extravasation site. Use a 25- or 27-gauge needle. Administer as soon as possible but within 12 hours of extravasation. Blanching should reverse immediately. Additional doses may be required if blanching returns.
Nitroglycerin 2% topical ointment	Vasodilates capillaries to reduce ischemia	Apply 1-inch strip to site of ischemia every 8 hours as needed.
Sodium thiosulfate	Reduces the formation of hydroxyl radicals which cause tissue injury	12.5 g IV over 30 minutes; may increase gradually to 25 g IV 3 times per week.

Table 5. Specific management of extravasation for various intravenous non-chemotherapeutic vesicants

Drug	Mechanism of Tissue Injury	Antidote	Thermal compress[4]
Acyclovir[4,5]	pH (11)	Hyaluronidase	Dry, warm compress
Aminophylline[1,4,5]	Osmolarity (170 mOsml/L)	Hyaluronidase	Dry, warm compress
Amiodarone[1,4,5]	pH (4.08)	Hyaluronidase	Dry, warm compress
Amphotericin[4,5]	Unknown; however pH 5-7	Hyaluronidase	Dry, cold compress for two days then warm compress
Ampicillin[4,5]	Osmolarity (50 mg/ml: 566 mOsml/kg)	Hyaluronidase	Dry, warm compress
Arginine[1,4,5]	pH (5.6) Hypertonicity Local hyperkalemia	Hyaluronidase	Dry, warm compress
Calcium chloride (≥ 10%)[1,4,5]	Osmolarity (10%: 2040 mOsml/L) Precipitation	Early/acute treatment (within hours): Hyaluronidase Delayed/late treatment (evidence of calcinosis cutis): Sodium thiosulfate	Dry, warm compress
Calcium gluconate[1,4,5]	Osmolarity (680 mOsml/L) Precipitation	Early/acute treatment (within hours): Hyaluronidase Delayed/late treatment (evidence of calcinosis cutis): Sodium thiosulfate	Dry, warm compress
Conivaptan[4,5]	pH (3.4-3.8)	Hyaluronidase	Dry, warm compress
Contrast media[1,5]	Osmolarity	Conflicting data regarding use of hyaluronidase as antidote. There are reports of successful use of hyaluronidase; however, the American College of Radiology does not recommend hyaluronidase.	Conflicting information for dry, warm vs dry, cold compresses.

Dantrolene[1,4]	pH (9.5-10.3)	Hyaluronidase	Dry, warm compress
Dextrose (≥ 10%)[1,4,5]	Osmolarity (10%: 505 mOsml/L)	Hyaluronidase	Dry, warm compress
Diazepam[4,5]	Osmolarity (>2000 mOsml/L)	Hyaluronidase	Dry, warm compress
Digoxin[4,5]	Osmolarity Cytotoxicity Vasoconstriction	Hyaluronidase	Dry, warm compress
Dobutamine[1,4,5]	Vasoconstriction Cytotoxicity	1st line: phentolamine 2nd line: terbutaline and/or topical nitroglycerin 2%	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).
Dopamine[1,4,5]	Vasoconstriction	1st line: phentolamine 2nd line: terbutaline and/or topical nitroglycerin 2%	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).
Doxycycline[4,5]	pH (1.8-3.3)	Hyaluronidase	Dry, warm compress
Epinephrine[1,4,5]	Vasoconstriction	1st line: phentolamine 2nd line: terbutaline and/or topical nitroglycerin 2%	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).
Esmolol[1,4]	pH (4.5-6.5)	Hyaluronidase	Dry, warm compress
Etomidate[4,5]	Osmolarity (4965 mOsml/L)	Hyaluronidase	Dry, warm compress
Gentamicin[4,5]	pH (3.5-5)	Hyaluronidase	Dry, warm compress
IVIG[4,5]	pH (4-7.2)	Hyaluronidase	Dry, warm compress
Lipids[4]	Absorption refractory pH (8.1) Osmolarity (356 mOsml/L)	Hyaluronidase	Dry, warm compress
Lorazepam[4,5]	Osmolarity (>2000 mOsml/L)	Hyaluronidase	Dry, warm compress
Mannitol[1,4,5]	Osmolarity (20%: 1100 mOsml/L)	Hyaluronidase	Dry, warm compress

Methylene blue[1,4,5]	Vasoconstriction Cytotoxicity pH (3-4.5)	1st line: topical nitroglycerin 2% 2nd line: phentolamine and/or terbutaline	Dry, warm compress
Metronidazole[4,5]	Unknown; however pH 4.5-7	Hyaluronidase	Dry, warm compress
Nafcillin[1,4,5]	Osmolarity (40mg/ml: 402 mOsml/L)	Hyaluronidase	Dry, warm compress
Nitroglycerin[5]	Osmolarity	Hyaluronidase	Dry, warm compress
Norepinephrine[1,4,5]	Vasoconstriction	1st line: phentolamine 2nd line: terbutaline and/or topical nitroglycerin 2%	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).
Penicillin[4,5]	Unknown; however pH 5-8.5	Hyaluronidase	Dry, warm compress
Pentamidine[1,4,5]	pH (4.5-7.5)	Hyaluronidase	Dry, warm compress
Pentobarbital[4]	pH (9-10.5)	Hyaluronidase	Dry, warm compress
Phenobarbital[4,5]	pH (9.2-10.2)	Hyaluronidase	Dry, warm compress
Phenylephrine[1,4,5]	Vasoconstriction	1st line: phentolamine 2nd line: terbutaline and/or topical nitroglycerin 2%	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).
Phenytoin[1,4,5]	pH (10-12.3) Precipitation	1st line: Hyaluronidase 2nd line: topical nitroglycerin 2%	Dry, warm compress
Piperacillin/Tazobactam[5]	Unknown	No known antidote	Dry, cold compress
Potassium acetate[1,4,5] **(>0.1 mEq/mL) ,potassium chloride**[,4,5] **(>0.1 mEq/mL)**, **potassium phosphate**[4,5]	Osmolarity (KCl 20meq/100ml: 400 mOsm/L, 40meq/100ml: 799 mOsml/L)	Hyaluronidase	Dry, warm compress
Promethazine[1,4,5]	pH (4-5.5) Cytotoxicity	1st line: Hyaluronidase 2nd line: topical nitroglycerin 2%	Dry, warm compress
Propofol[4,5]	pH (6-8.5) Absorption refractory	Hyaluronidase	Dry, warm compress

Sodium bicarbonate (≥8.4%)[1,4,5]	Osmolarity (8.4%: 2000 mOsml/L)	Hyaluronidase	Dry, warm compress
Sodium chloride (> 1%)[1,4]	Osmolarity (0.9%: 308 mOsm/L, 3%: 839 mOsml/L)	Hyaluronidase	Dry, warm compress
Sodium phosphate[4]	Osmolarity (7000 mOsml/L)	Hyaluronidase	Dry, warm compress
TPN[1,4,5]	Osmolarity (>900 mOsml/L)	1st line: Hyaluronidase 2nd line: topical nitroglycerin 2%	Dry, warm compress
Valproate[4,5]	Toxicity to skin structures is proposed mechanism	Hyaluronidase	Dry, cold compress
Vancomycin[4,5]	pH (2.5-4.5)	Hyaluronidase	Dry, warm compress
Vasopressin[1,4,5]	Vasoconstriction	1st line: topical nitroglycerin 2% 2nd line: phentolamine and/or terbutaline	Dry, warm compress. Avoid ice packs, conivaptan, and hyaluronidase (may worsen vasoconstriction).

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