Extravasation

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Thank You AVA

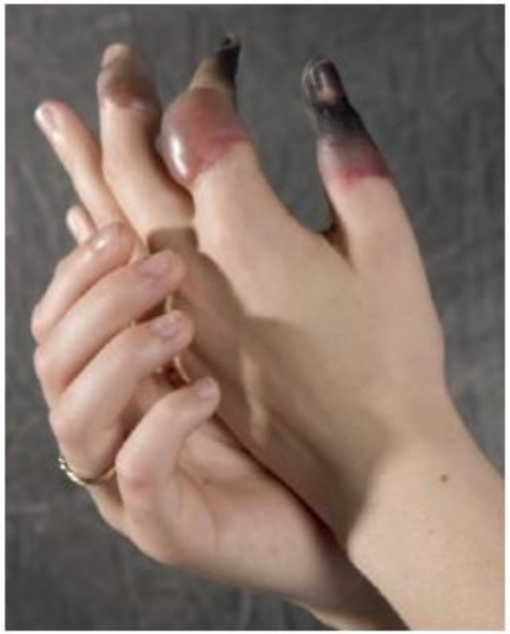
- Things we are talking about
  - Extravasation
  - CONGRATULATIONS TO BRANDON, NEXT INCOMING PRESIDENT
  - Let’s Go Brandon

Thank you AVA

- Things we are NOT talking about
  - Heparin Flush NBO
  - Ethanol lock
  - Heparin/Vanco lock
  - When is a PICC not a PICC
  - Global Warming
  - Jan’s Guide to getting a car out of NYC impound

Promethazine

*In 2005, a 19-year-old woman went to the emergency department with flu-like symptoms and received the branded drug Phenergan IV.[1] During the injection, she yelled out in pain and was tempted to pull out her IV line. After the injection, she told the nurse that her arm was still in significant pain and that she felt "something was wrong." The nurse reassured the patient and left the room. The patient's arm and fingers became purple and blotchy. The patient remained in the hospital for 30 days, during which she watched her previously healthy fingers turn black and shrivel (see **Figure 1**). Her thumb, index finger, and top of her middle finger had to be amputated.*



Phenergan extravasation caused gangrene in a young woman's fingers.
(Courtesy of The Daily World, Aberdeen, WA)

Action Needed to Prevent Serious Tissue Injury with IV Promethazine

August 10, 2006

Patrick J. Marshfield woman wins 7.4 million jury award after she loses arm. The Barre Montpelier Times Argus; Barre, VT; March 19, 2004

Bonus Round

BEST PRACTICE 13:

Eliminate injectable promethazine from the formulary.

- Remove injectable promethazine from all areas of the organization including the pharmacy.
- Classify injectable promethazine as a non-stocked, non-formulary medication.
- Implement a medical staff-approved automatic therapeutic substitution policy to convert all injectable promethazine orders to another antiemetic.
- Remove injectable promethazine from all medication order screens, and from all order sets and protocols.

This Best Practice includes not using intramuscular administration of promethazine because this can also cause tissue damage if accidentally injected intraarterially.

Rationale:

The goal of this Best Practice is to eliminate the risk of serious tissue injuries and amputations from the inadvertent arterial injection or IV extravasation of injectable promethazine. ISMP brought attention to this serious issue in August 2006 and conducted a survey to determine the prevalence of the issue. Of the nearly 1,000 responses to the survey, 1 in 5 reported awareness of such an occurrence in their facility during the prior 5 years. The US Food and Drug Administration (FDA) requires the manufacturer to include strong warnings about the risk of inadvertent intraarterial injection or perivascular extravasation of this drug in the package insert. Injectable promethazine has been included on the *ISMP List of High-Alert Medications in Acute Care Settings* (www.ismp.org/node/103) since 2007.

In 2009, ISMP recommended removal of injectable promethazine from an organization's formulary, if possible, and use of safer alternatives such as 5-HT_3 antagonists (e.g., ondansetron). However, these products were significantly higher in cost at the time. Since then, these alternative injectable antiemetics have become available as generic products and are significantly less costly. Thus, injectable promethazine has been used less frequently, and for safety, should now be removed from all formularies.

Best Practice 13 First Introduced:

2018-2019

Related *ISMP Medication Safety Alerts!*:

June 27, 2013; October 8, 2009; September 24, 2009; October 9, 2008; November 2, 2006; **August 10, 2006**.

Treatment - Promethazine

Extravasated Medication	Preferred Antidote	Antidote Administration	Supportive Management	Comments	ADDITIONAL COMMENTS	pH	mOsmol/L (Unless stated otherwise)
Promethazine	No known antidote	No known antidote	Information conflicts: Apply dry cold (Hurst 2004) or dry warm compresses (Reynolds 2014)	Note: Preferred route of administration for promethazine is by deep intramuscular (IM) injection. If IV route is used, discontinue infusion immediately with onset of burning/pain; evaluate for inadvertent arterial injection or extravasation.	RISK-VESICANT. Elevate Extremity.	4-5.5	291 mOsmol/kg

Title and Content Layout with List

- Define extravasation
- Types of extravasation agents
- Become familiar with INS Guidelines
- Be able to apply proper treatment for specific type of extravasating agent

Definitions

- **Extravasation:** Unintentional or inadvertent leakage (or instillation) of fluid (medication) out of a blood vessel into surrounding tissue

  - Differs from infiltration
    - **Type of medicine or fluid that is leaked.** Infiltration
    - If fluid is a non-vesicant (does not irritate tissue)

Management of Drug Extravasation; Lexicomp

Definitions

- Extravasation injury
  - Defined as the damage caused by the efflux of solutions from a vessel into surrounding tissue spaces during intravenous infusion.
  - Damage can extend to involve nerves, tendons, and joints
  - Can continue for months after the initial insult
  - If treatment is delayed, surgical debridement, skin grafting, and even amputation may be the unfortunate consequences of such an injury.

Extravasation Injuries in Adults ISRN Dermatol, 2013: 2013: 856541

Types of Extravasated Agents

- Extravasated drugs are classified according to their potential for causing damage
  - Primary Classification
    - Vesicant
    - Irritant or Non-vesicant
- Classifications are not rigid
  - An agent may demonstrate irritant potential but could be a vesicant in larger doses

NIHJournal List Pediatr Rep v.4(3); 2012 Jul 31 PMC4227315

Types of Extravasated Agents - Vesicant

- **Vesicant:** Extravasation of a vesicant drug has the potential to cause tissue necrosis (blistering, sloughing of tissue, and varying degrees of deep tissue damage)
  - Generally
    - Chemotherapy
    - Non-chemotherapy

Extravasation injury from chemotherapy and other non-antineoplastic vesicants Jan 02, 2020

Types of Extravasated Agents - Vesicant

- **Vesicant Chemotherapeutic agents further categorized**
  - **Non-DNA Binding** - are metabolized and neutralized in the tissues Journal List Pediatr Rep v.4(3); 2012 Jul 31PMC4227315

Non-DNA Binding	
Alkylators	Amsacrine
Plant alkaloids	Vinblastine, vincristine, vindesine, vinorelbine
Taxanes	Docetaxel, paclitaxel (note: considered to be mild vesicants)

Elsevier. In: Schulmeister L. Extravasation management. Semin Oncol Nurs. 2007;23:184-190.

Types of Extravasated Agents - Vesicant

- **DNA Binding** - anthracyclines (ie. Doxorubicin) set up a continuous cycle of tissue damage that is mediated by medication cellular DNA, resulting in more extensive injuries

DNA Binding	
Alkylating agents	Mechlorethamine (nitrogen mustard)
Anthracycline antibiotics	Daunorubicin, doxorubicin, epirubicin, idarubicin
Other anticancer antibiotics	Dactinomycin, mitomycin, mitoxantrone

Elsevier. In: Schulmeister L. Extravasation management. Semin Oncol Nurs. 2007;23:184-190.

Types of Extravasated Agents - Vesicant

- Damage MOA
  - Drug is absorbed by local cells in the tissue and binds to critical structures (*e.g.* DNA, microtubules), causing cell death.
  - After the endocytolysis, surrounding cells can also die through the release of the drug from nearby dead cells.
  - The repetitive nature of this process impairs healing and may result in progressive and chronic tissue injury

Types of Extravasated Agents

Antineoplastic drugs that act as vesicants or irritants

Vesicants
Amsacrine
Dactinomycin
Daunorubicin
Doxorubicin
Enfortumab vedotin
Epirubicin
Idarubicin
Mechlorethamine
Mitomycin
Trabectedin
Vinblastine
Vincristine and liposomal vincristine
Vindesine
Vinorelbine

Types of Extravasated Agents - Vesicant

- Non-Chemotherapy
  - pH mediated tissue injury
  - Osmolarity mediated tissue injury
  - Vasoconstriction mediated tissue injury
  - Absorption refractory mediated tissue injury
  - Unknown mechanism of tissue injury

Types of Extravasated Agents - Vesicant

- **Nonphysiologic pH**
  - Physiologic pH is 7.35–7.45
  - pH of <5 or >9, 10 can damage venous endothelium
  - Increase risk of vessel rupture
  - Cause damage with tissue destruction and vasoconstriction
  - Resulting inflammatory response, edema, sloughing,
  - Ulceration may result
  - Neutralization of extreme pH should not be attempted because of the potential for exothermic or gas-producing reactions that may exacerbate the injury

Types of Extravasated Agents - Vesicant

Vesicant	Antidote recommendations	Antidote cases	Other treatments
pH mediated tissue injury			
Acyclovir: pH 11[43]	Hyaluronidase[13,49]	Hyaluronidase, flush out, and aspiration: 7 cases had no injury.[85]	Conservative: 5 of 10 cases necrosed, including 1 that required surgery; 4 cases vesiculated and 1 had no injury.[182-189]
Amiodarone: pH 4.08[43]	Hyaluronidase[13,56]	Hyaluronidase: no injury in 2 cases where dry heat was inadequate.[190]	Conservative: 2 cases necrosed, including 1 that required surgery and had PFD.[191,192]
Arginine: pH 5.6[3] Hypertonicity[193] and local hyperkalemia[194] are additional mechanisms of tissue injury	Hyaluronidase for acid/base vesicants[13]		Conservative: 4 cases necrosed including 2 that required surgery.[193-196]
Conivaptan: pH 3.4-3.8[43]	Hyaluronidase[13]		
Dantrolene: pH 9.5-10.3[43]	Hyaluronidase for acid/base vesicants[13]		
Doxycycline: pH 1.8-3.3[43]	Hyaluronidase[13]		
Esmolol: pH 4.5-6.5[43]	Hyaluronidase for acid/base vesicants[13]	Hyaluronidase, flush out, and aspiration: Necrosis from unspecified "beta blocker."[59]	
Gentamicin: pH 3-5.5[43]	Hyaluronidase[13,48-50]		Conservative: 3 cases necrosed; 2 were co-extravasations with penicillin.[23,72,99]

Types of Extravasated Agents - Vesicant

- **Osmolarity**
  - Physiologic osmolarity is approximately 310 mOsm/L
  - Hypotonic and hypertonic solutions can cause tissue damage by forcing fluid shifts into or out of cells.
    - Hypotonicity
      - Causes fluid shift into cells, which can result in cell rupture
      - Low range risk of hemolysis <112 mOsm/L
    - Hypertonicity
      - Disrupts cellular ion transport causing fluid shift from cells to the interstitial space
      - May lead to swelling and compartment syndrome
      - High range risk of being a vesicant >900 mOsm/L

Types of Extravasated Agents - Vesicant

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants

Vesicant	Antidote recommendations	Antidote cases	Other treatments
Osmolarity mediated tissue injury			
Aminophylline: 170 mOsm/L[43]	Hyaluronidase[13,44-49]	Hyaluronidase: at least 1 case of injury prevention[44,45]	
Ampicillin 50 mg/mL: 566 mOsm/kg [10]	Hyaluronidase[13,48-50]	Hyaluronidase: 1 co-extravasation with cefotaxime in dextrose 10% and 0.225% saline necrosed.[51]	Conservative: 1 co-extravasation with chloramphenicol necrosed with PFD.[52]
Calcium salts, including calcium disodium edetate (EDTA) Calcium chloride 10%: 2040 mOsm/L[43] Precipitation is an additional mechanism of injury[53]	Early treatment: Hyaluronidase[13,44-49,54-56] Alternative: sodium thiosulfate[57,58]	Hyaluronidase: 4 of 10 cases necrosed, 2 of which had delayed administration; the severest case had surgery.[6,44,59-61] Hyaluronidase, flush out and aspiration: 1 case without injury.[59]	Saline flush out: 1 calcinosis cutis case necrosed and required surgery (a co-extravasation with parenteral nutrition).[62] Conservative: all 43 cases necrosed, including 2 with calcinosis cutis and 25 cases requiring surgery of which 9 had PFD.[17,44,53,63-80]
Calcium salts, including calcium disodium edetate (EDTA) Calcinosis cutis without necrosis	Monitor superficial calcifications closely as many resolve spontaneously.[13] Alternative: sodium thiosulfate[13,58]		Prednisone: calcium deposits persisted at 1 y[81] Conservative: 6 cases of which 2 resolved over months, 1 required surgery and 3 had no reported outcome.[53,74,82,83]
Calcium gluconate or calcium gluceptate: 680 mOsm/L[43] Precipitation is an additional mechanism of injury[53]	Early treatment: Hyaluronidase[13,44-46,48,49,54,56] Alternative: sodium thiosulfate[57,58]	Hyaluronidase: 1 case of necrosis where treatment mitigated damage.[84] Hyaluronidase, flush out, and aspiration: 3 cases without necrosis[85]	Flush out and aspiration: 9 cases necrosed.[86] Conservative: 39 cases necrosed, including 28 cases that required surgery with 8 cases of PFD. One nonsurgical case had PFD.[17,23,57,63,64,72,78,87-101]

Types of Extravasated Agents - Vesicant

- **Vasoconstriction**
  - Localized vasoconstriction can result in ischemia and necrosis by reducing blood flow
  - Vesicant exposed tissues are at risk from both chemically induced and mechanically induced vasoconstriction
    - Chemically induced
      - Electrolyte solutions such as calcium and sodium
      - pharmacologic vasopressors such as dopamine and epinephrine
    - Mechanically induced
      - Large volume or anatomically trapped extravasations can vasoconstriction when the interstitial pressure is raised enough to overcome the venous pressure, blocking blood flow and even causing compartment syndrome.

Types of Extravasated Agents - Vesicant

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
Vasoconstriction mediated tissue injury			
Dobutamine Cytotoxicity is an additional mechanism of injury[3,127]	First line: phentolamine[13,46-49,56,58,233,236] Second line: terbutaline or nitroglycerin[13,46,58]	Terbutaline: 1 case without damage (a co-extravasation with dopamine).[233]	Conservative: 9 of 10 cases necrosed including 4 surgery cases with 1 PFD.[41,99,122,234,235]
Dopamine	First line: phentolamine[13,45-50,56,58,230,236] Second line: terbutaline[13,231,233] or nitroglycerin[13,46,58,231,233]	Phentolamine: 1 of 20 cases necrosed.[237-241] Phentolamine with nitroglycerin: 4 cases without necrosis, including 1 case of administration of nitroglycerin after inadequate response to phentolamine.[242,243] Phentolamine and papaverine: 1 case with functional deficit.[244] Nitroglycerin topical: 5 cases of which 4 were without necrosis. The necrosis case was an epinephrine co-extravasation that had surgery.[242,245-247]	Hyaluronidase, flush out, and aspiration: 1 of 7 cases necrosed, likely due to treatment delay of 6 h.[59] Flush out with aspiration: 2 cases without injury.[59] Conservative: 9 of 20 cases necrosed and required surgery, including 4 with PFD.[64,246,248-251]
Epinephrine	First line: phentolamine[13,45-50,56,58,231,233,236] Second line: terbutaline[13,231] or nitroglycerin[13,46,58]	Lidocaine with epinephrine in digits: phentolamine (n = 54) vs saline (n = 54) had faster return of color (85 vs 319 min) and sensation (120 vs 549 min); no necrosis developed.[252] Phentolamine administered after amyl nitrate inhalations were inadequate in a finger laceration exposed to topical epinephrine (1 case)[253] Autoinjector exposure with full symptom resolution (# of cases): • Phentolamine (12)[254-263] • Phentolamine and oral nifedipine (1)[264] • Phentolamine with lidocaine nerve block (2)[265,266] • Nitroglycerin: 6 cases including 1 sublingual[256,258,267,268] • Nitroglycerin and terbutaline (3)[233,258] • Nitroglycerin and lidocaine nerve block (1)[257] Phentolamine rescue therapy after failed therapy with: • Nitroglycerin (2)[258,269] • Nitroglycerin with lidocaine nerve block (1)[270] • Nitroglycerin, topical, with nifedipine sublingual (1)[271] • Terbutaline (1)[233]	Hyaluronidase, flush out, and aspiration: a co-extravasation with calcium gluconate, 50% dextrose, albumin, and sodium bicarbonate had no necrosis[100] Pentoxyphilline: 1 case necrosed.[272] Conservative: 5 cases necrosed, including 1 co-extravasation with aramine and 1 with sodium bicarbonate. Of the 5 cases, 4 required surgery with 2 cases of PFD.[64,151,167,177] Epinephrine (with or without lidocaine) in digits with conservative treatment: 8 cases with eventual full resolution; 1 case with 10 wk of impaired sensation and pain.[273] Autoinjector Exposure, symptoms resolved: • Iloprost intravenous with Stellate ganglion block in 1 case.[274] • Nifedipine oral in 1 case.[257] • Conservative: 9 cases[256-258,273]

Types of Extravasated Agents - Vesicant

- **Absorption Refractory**
  - Newly proposed mechanism of tissue injury whereby drugs with insolubilities or limited ability to be absorbed into the bloodstream persist in the extravasated space.
  - Prolonged presence of lipids in the interstitial space has led to deep tissue necrosis
    - Propofol, often contained in a lipid carrier solution, seems particularly prone to causing necrosis and compartment syndrome

Types of Extravasated Agents - Vesicant

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
Absorption refractory mediated tissue injury			
Lipids: pH 8.1[10] 356 mOsm/kg[10]	Authors recommend: Hyaluronidase and consider flush out.		Conservative: 1 case of necrosis required surgery.[23]
Propofol: pH 6.0-8.5[226] Isotonic[226]	Authors recommend: hyaluronidase and consider flush out.	Hyaluronidase, flush out, and drains: 2 cases without necrosis including a co-extravasation with analgesics and Hartmann's solution and a case with inadequate response to hyaluronidase.[25,36]	Compartment syndrome: 4 cases with surgery.[32,33,35] Conservative: 6 of 7 cases necrosed including 4 that required surgery.[24,26,27,29-31,34]

Types of Extravasated Agents - Irritants

- **Irritant or Non-vesicants**: cause inflammation (warmth, erythema, tenderness) at the administration site and along the vein, but they rarely result in direct toxicity to the tissue (ie, necrosis) [10]. Some irritants can cause tissue necrosis if large volumes of concentrated solutions have extravasated.

UpToDate Extravasation injury from chemotherapy and other non-antineoplastic vesicants

Types of Extravasated Agents - Irritants

Irritants	
Ado-trastuzumab emtansine*	Gemcitabine
Bendamustine¶	Ifosfamide
Bleomycin	Irinotecan¶
Bortezomib	Ixabepilone
Busulfan	Liposomal daunorubicin¶
Carboplatin	Liposomal doxorubicin¶
Carmustine	Melphalan¶
CisplatinΔ	Mitoxantrone¶
Cladribine	Oxaliplatin¶
Cyclophosphamide	Paclitaxel¶
Cytarabine	Paclitaxel, nanoparticle albumin bound (nabpaclitaxel)
DacarbazineΔ	
Docetaxel	Streptozocin
Etoposide	Teniposide
Fluorouracil/floxuridine	Topotecan

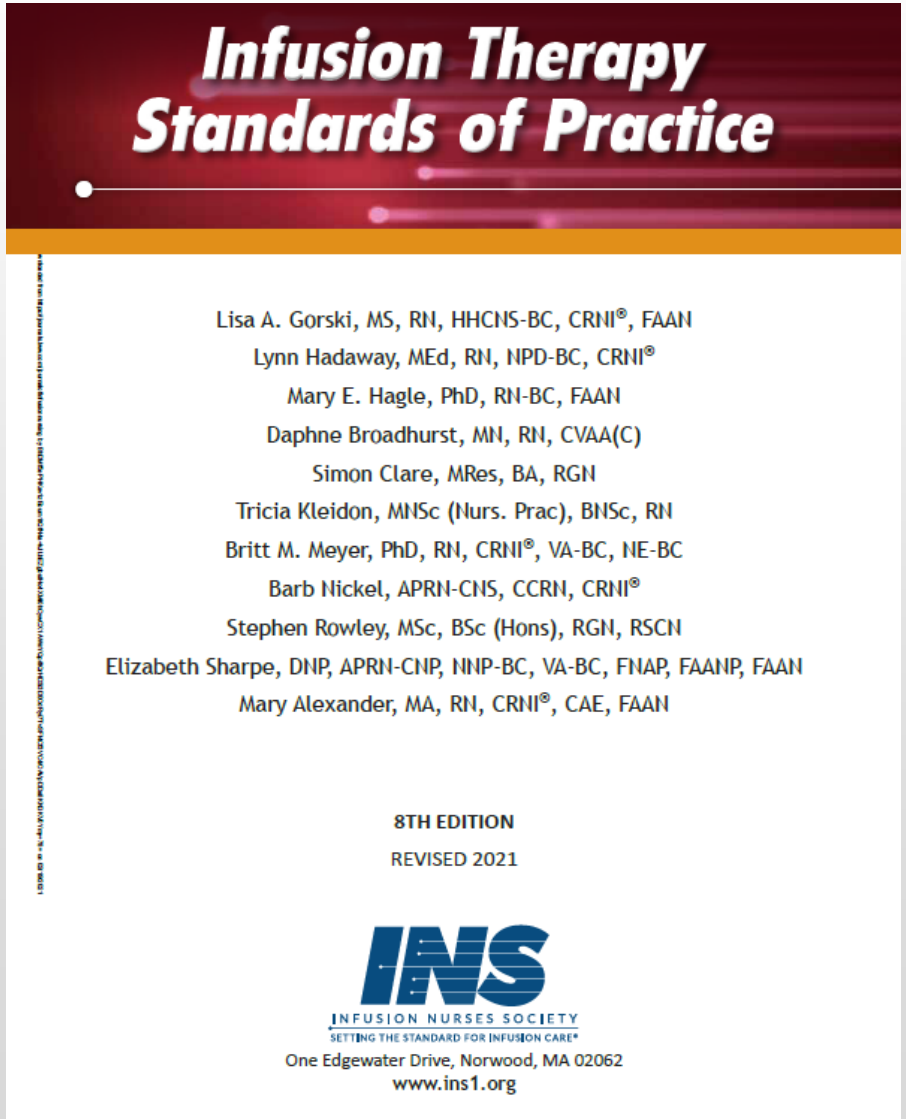
Prevention

- Prevention is the most IMPORTANT Extravasation management
- Few precautions minimize risk
  - USE CVC if present or large vein
  - Intact vessel with good blood flow
  - Veins in the forearm (ie, basilic, cephalic, and median antebrachial) are usually good options for peripheral infusions. To minimize the risk of dislodging the catheter
  - **AVOID** using veins in the hands, dorsum of the foot, and any joint space (eg, antecubital).
  - It is important to remember to not administer chemotherapy distal to a recent venipuncture.
- Patient immediately report any signs of pain, itching, tingling, burning, redness, swelling, or discomfort, all of which could be early signs of extravasation. Symptoms of extravasation which may appear later include blistering, ulceration, and necrosis.
- Ensure the health care team is informed of the risks and management strategies for both prevention and treatment of extravasations. Absence of blood return, resistance upon administration, or interruption of the IV flow should raise suspicion of potential extravasation.

Management: non-pharmacologic

- **Stop the infusion:** At the first suspicion of extravasation, the drug infusion and IV fluids should be stopped.
- **Do NOT remove the catheter/needle:** The IV tubing should be disconnected, but the catheter/needle should be left in place to facilitate aspiration of fluid from the extravasation site and, if appropriate, administration of an antidote.
- **Aspirate fluid:** To the extent possible, the extravasated drug solution should gently be removed from the subcutaneous tissues. It is important to avoid any friction or pressure to the area. Aspiration of extravasated contrast media is not recommended.
- **Do NOT flush the line:** Flooding the infiltration site with normal saline or dextrose (5%) in an attempt to dilute the drug solution is not recommended.
- **Remove the catheter/needle:** If an antidote is not going to be administered into the extravasation site, the catheter/needle should be removed. If an antidote is to be injected into the area, it should be injected through the catheter to ensure delivery of the antidote to the extravasation site. When this has been accomplished, the catheter should then be removed.
- **Elevate:** The affected extremity should be elevated.
- **Compresses:** If indicated, apply dry compress to area of extravasation (either cold or warm, depending on vesicant extravasated).
- **Monitor and document:** Mark the extravasation site (using a surgical felt pen, gently draw an outline on the skin of the extravasation area) and photograph if possible. Monitor and document the event and follow-up activities according to institutional policy.

INS 2021 Guidelines



Treatment

- Recognize the differences among vesicant, nonvesicant,
- Identify the vesicant nature of cytotoxic and noncytotoxic medications prior to administration
- Be prepared to use the correct pharmacologic and nonpharmacologic treatment in the event of extravasation
- Escalate to a clinician capable of managing these injuries

Infusion Therapy Standards of Practice 8th Edition Revised 2021 INS

Treatment - Vesicants

- DNA Binding Agents
  - Apply dry, cold compress
  - Goal is to cause vasoconstriction
  - Localize the medication in the tissue and reduce inflammation
  - Remove the cold compress 15 minutes before the infusion of Dexrazoxane begins

Treatment - Vesicants

Extravasated Medication	Preferred Antidote	Antidote Administration	Supportive Management	Comments	ADDITIONAL COMMENTS	pH	mOsmol/L (Unless stated otherwise)
DAUNOrubicin (Conventional)	Dexrazoxane or topical Dimethyl Sulfoxide (DMSO)	Adults: Dexrazoxane 1,000 mg/m^2 (maximum dose: 2,000 mg) IV (administer in a large vein remote from site of extravasation) over 1 to 2 hours days 1 and 2, then 500 mg/m^2 (maximum dose: 1,000 mg) IV over 1 to 2 hours day 3; begin within 6 hours after extravasation (Mouridsen 2007; Pérez Fidalgo 2012). Note: Reduce dexrazoxane dose by 50% in patients with moderate to severe renal impairment (CrCl <40 mL/min). Pediatrics and Adults: DMSO: Apply topically to a region covering twice the affected area every 8 hours for 7 days; begin within 10 minutes of extravasation; do not cover with a dressing (Pérez Fidalgo 2012)	Apply dry cold compress for 20 minutes 4 times/day for 1 to 2 days (Pérez Fidalgo 2012). Withhold cooling for 15 minutes before and after dexrazoxane.	If using dexrazoxane, do not use DMSO. Administer dexrazoxane through a large vein remote from area of the extravasation.	Daily IV infusion of dexrazoxane over 3 days is the recommended antidote for anthracycline extravasation. 1)Begin infusion within 6 hours of the extravasation and infuse into the opposite extremity. 2)Topical dimethyl sulfoxide (DMSO) should not be applied to patients receiving dexrazoxane as it may diminish dexrazoxane efficacy. RISK-VESICANT	~9.5-10.3	~261

Treatment - Vesicants

- Non-DNA Binding Agents
  - Apply dry, warm compress
  - Encourages vasodilation
  - Goal is to increase local blood flow
  - Disperse the medication through the tissue
  - Administer Hyaluronidase

Treatment - Vesicants

Extravasated Medication	Preferred Antidote	Antidote Administration	Supportive Management	Comments	ADDITIONAL COMMENTS	pH	mOsmol/L (Unless stated otherwise)
VinCRIStine (Conventional)	Hyaluronidase	Hyaluronidase: *If needle/cannula still in place:* Administer 1 to 6 mL (150 units/mL) into existing IV line; usual dose is 1 mL for each 1 mL of extravasated drug (Pérez Fidalgo 2012; Schulmeister 2011) *If needle/cannula was removed:* Inject 1 to 6 mL (150 units/mL) subcutaneously in a clockwise manner using 1 mL for each 1 mL of drug extravasated (Schulmeister 2011) or administer 1 mL (150 units/mL) as five separate 0.2 mL injections (using a 25-gauge needle) into the extravasation site (Polovich 2009)	Apply dry warm compress for 20 minutes 4 times/day for 1 to 2 days (Pérez Fidalgo 2012)		RISK-VESICANT. El	3.5-5	286

Treatment - Vasopressors

- Phentolamine is preferred for vasopressor extravasation. Normal perfusion of the area may be seen within 10 minutes. Repeated injection may be necessary if hypoperfusion is still present or if vasoconstriction is extending to a greater area.
- Terbutaline injection has been used for vasopressor extravasation when phentolamine is not immediately available.
- Topical nitroglycerin 2% may be applied as a 1-inch strip to the site of vasopressor extravasation in absence of phentolamine; repeat every 8 hours as clinically indicated.

Treatment - pH

- Use nonpharmacologic methods (eg, elevation, surgical washout) for extravasation of acidic and alkaline medications.
- Avoid injection of an acidic or alkaline medication in an attempt to neutralize the pH of an extravasated acidic or alkaline vesicant as the resulting chemical reaction could cause gas formation and exacerbate the tissue injury.

Treatment – Irrigation

- Consider subcutaneous saline irrigation or saline irrigation with prior hyaluronidase administration for vesicant removal/dispersion in neonates

Treatment - Hyaluronidase

- Is not considered to be an antidote to a specific vesicant
- Enzyme that increases absorption and dispersion of the medication or solution in the tissue and its use is reported with cytotoxic and noncytotoxic drugs
- Including both acidic and alkalotic drugs (eg, amiodarone and phenytoin), as well as hyperosmolar solutions (eg, parenteral nutrition [PN] and calcium salts).
- Recombinant hyaluronidase is not derived from animals and may have a lower risk of allergic response.
- Subcutaneous injection within 1 hour of the extravasation event produces the best response. Do not inject by the intravenous (IV) route.
- Use of dry heat in conjunction with hyaluronidase works synergistically to increase blood flow and disperse the extravasated drug
- Most used treatment, benign

Treatment – Steroids

- Consider use of oral, topical, or intralesional steroid on a case-by-case basis.
- Single-center studies and case reports have reported reduced inflammation and swelling; however, evidence of benefit is limited and inconsistent.
- Glucocorticoids are presumed to reduce local inflammation, but it has never been shown that tissue damage from vesicant extravasation is the result of an inflammatory process. In general, glucocorticoids are not indicated in the management of vesicant extravasations, with the possible exception of large-volume extravasations of oxaliplatin. This position is consistent with recommendations from the ONS and EONS [2,20]. Glucocorticoids may worsen the skin damage from etoposide or vinca alkaloids, and they are specifically contraindicated in these situations.

Treatment – Surgical Intervention

- The need for surgical consultation is based on the clinical signs and symptoms and their progression (eg, compartment syndrome from infiltration of a nonvesicant medication) and/or the tissue-destroying nature of a vesicant medication.
- Options for treatment include subcutaneous irrigation with or without hyaluronidase, open incision and irrigation, small incisions followed by massage to force drainage, and debridement; skin grafting may be indicated.

Treatment : Lexi-Drugs

Management of Drug Extravasations (Lexi-Drugs)

Management of Drug Extravasations

Table 1: Vesicant Agents[a] and Extravasation Management

Extravasated Medication	Preferred Antidote	Antidote Administration	Supportive Management	Comments
Amino Acids (4.25%)/parenteral nutrition	Hyaluronidase	Hyaluronidase: Intradermal or SubQ: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections (using a 25-gauge needle) into area of extravasation at the leading edge in a clockwise manner (MacCara 1983; Reynolds 2014; Zenk 1981)	Apply dry cold compresses (Hurst 2004)	
Aminophylline	Hyaluronidase	Hyaluronidase: Intradermal or SubQ: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections (using a 25-gauge needle) into area of extravasation at the leading edge in a clockwise manner (MacCara 1983; Reynolds 2014; Zenk 1981)	Apply dry cold compresses (Hurst 2004; Reynolds 2014)	
Amiodarone	Hyaluronidase	Hyaluronidase: May consider for refractory cases in addition to supportive management (Reynolds 2014) Intradermal: Inject five separate 0.2 mL injections of 15 units/mL (using a 25-gauge needle) into area of extravasation (Fox 2017)	Apply dry warm compresses (Reynolds 2014)	May be a vesicant
Amsacrine	No known antidote	No known antidote	Apply dry warm compresses (Schulmeister 2011)	Irritant with vesicant-like properties (reports of both irritant and vesicant reactions) Not commercially available in the US
Arginine	Hyaluronidase	Hyaluronidase: Intradermal: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections to border of extravasation area (Reynolds 2014)	Apply dry cold compresses (Reynolds 2014)	Irritant with vesicant-like properties (reports of both irritant and vesicant reactions)
Bendamustine	Sodium Thiosulfate	May be managed in the same manner as mechlorethamine extravasation (Schulmeister 2011): Sodium thiosulfate $^1/_6$ M solution: Inject subcutaneously into extravasation area using 2 mL for each mg of mechlorethamine suspected to have extravasated (Pérez Fidalgo	Apply dry cold compresses for 20 minutes 4 times/day for 1 to 2 days (Pérez Fidalgo 2012)	Irritant with vesicant-like properties (reports of both irritant and vesicant reactions)

Treatment – DRAFT Extravasation Table

Table 1: Vesicant Agents and Extravasation Management

Extravasated Medication	Preferred Antidote	Antidote Administration	Supportive Management	Comments	ADDITIONAL COMMENTS	pH	mOsmol/L (Unless stated otherwise)
Amino Acids (4.25%)/parenteral nutrition	Hyaluronidase	Hyaluronidase: Intradermal or SubQ: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections (using a 25- gauge needle) into area of extravasation at the leading edge in a clockwise manner (MacCara 1983; Reynolds 2014; Zenk 1981)	Apply dry cold compresses (Hurst 2004)		Alternative therapy- Nitroglycerin topical 2% ointment. (Apply one inch strip to site of ischemia, may repeat after 8 hours if needed.) RISK-VESICANT. Elevate Extremity.		
Aminophylline	Hyaluronidase	Hyaluronidase: Intradermal or SubQ: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections (using a 25- gauge needle) into area of extravasation at the leading edge in a clockwise manner (MacCara 1983; Reynolds 2014; Zenk 1981)	Apply dry cold compresses (Hurst 2004; Reynolds 2014)		RISK-VESICANT. Elevate Extremity.	8.6-9	170
Amiodarone	Hyaluronidase	Hyaluronidase: May consider for refractory cases in addition to supportive management (Reynolds 2014) Intradermal: Inject five separate 0.2 mL injections of 15 units/mL (using a 25-gauge needle) into area of extravasation (Fox 2017)	Apply dry warm compresses (Reynolds 2014)	May be a vesicant	Elevate Extremity.		
Amsacrine	No known antidote	No known antidote	Apply dry warm compresses (Schulmeister 2011)	Irritant with vesicant- like properties (reports of both irritant and vesicant reactions) Not commercially available in the US	Stop infusion immediately, discconect, leaving needle in place; Gently aspirate, DO NOT FLUSH LINE. Elevate Extremity.	3.5-4.5	280-320 mOsmol/kg
Arginine	Hyaluronidase	Hyaluronidase: Intradermal: Inject a total of 1 to 1.7 mL (15 units/mL) as five separate 0.2 to 0.3 mL injections to border of extravasation area (Reynolds 2014)	Apply dry cold compresses (Reynolds 2014)	Irritant with vesicant- like properties (reports of both irritant and vesicant reactions)		7.2	>600
Bendamustine	Sodium Thiosulfate	May be managed in the same manner as mechlorethamine extravasation (Schulmeister 2011): Sodium thiosulfate $^{1}/_{6}$ M solution: Inject subcutaneously into extravasation area using 2 mL for each mg of mechlorethamine suspected to have extravasated (Pérez Fidalgo 2012; Polovich 2009)	Apply dry cold compresses for 20 minutes 4 times/day for 1 to 2 days (Pérez Fidalgo 2012)	Irritant with vesicant- like properties (reports of both irritant and vesicant reactions)	Monitor for erythema, swelling, and pain from extravasation. Elevate Extremity.	5.6	950 mOsmol/L

Treatment - MOA

- Dexrazoxane
  - Derivative of ethylenediaminetetraacetic acid (EDTA)
  - Potent intracellular chelating agent.
  - Management of anthracycline extravasation, may act by reversibly inhibiting topoisomerase II, protecting tissue from anthracycline cytotoxicity, thereby decreasing tissue damage.

Management of Drug Extravasations (Lexi-Drugs)

Treatment - MOA

- DMSO Dimethyl Sulfoxide
  - Free-radical scavenger properties, which increases removal of vesicant drugs from tissues to minimize tissue damage in extravasation management (ESMO/EONS [Pérez Fidalgo 2012]).

Treatment - MOA

- Hyaluronidase
  - Enzymatically modifies the permeability of connective tissue through hydrolysis of hyaluronic acid, one of the chief components of tissue cement which offers resistance to diffusion of liquids through tissues; hyaluronidase increases the distribution/dispersion and absorption of locally injected or extravasated IV medications

Management of Drug Extravasations (Lexi-Drugs)

Treatment - MOA

- Phentolamine
- Competitively blocks alpha-adrenergic receptors (nonselective) to produce brief antagonism of circulating epinephrine and norepinephrine to reduce hypertension caused by alpha effects of these catecholamines and minimizes tissue injury due to extravasation of these and other sympathomimetic vasoconstrictors (eg, dopamine, phenylephrine);

Management of Drug Extravasations (Lexi-Drugs)

Treatment - MOA

- Sodium Thiosulfate
  - Extravasation management: Neutralizes the reactive species of mechlorethamine; reduces the formation of hydroxyl radicals which cause tissue injury

Treatment - MOA

- Terbutaline
  - Terbutaline and topical nitroglycerin have been used (case reports) as alternatives to phentolamine in the event of phentolamine supply shortages. Topical nitroglycerin (2% ointment) is reported to reverse the vasoconstriction at the extravasation site caused by infiltration of sympathomimetic vasoconstrictors; case reports for use in neonates/infants suggest resolution of ischemia (Denkler 1989; Wong 1992).

Management of Drug Extravasations (Lexi-Drugs)

Discussion

THANK YOU FOR YOUR TIME

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