Extravasation Management: A Hot Problem With Cold Solutions

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Disclosure
- Relevant Financial Conflicts of Interest
  - CE Presenter, Graham Klink, PharmD
    - None
  - CE Mentor, Erik Harrington, MS, PharmD, BCOP
    - None
  - CE Mentor, Nannette Sageser, PharmD
    - None
- Off-Label Uses of Medications
  - Sodium thiosulfate
  - Phentolamine
  - Hyaluronidase
  - Dimethyl sulfoxide
  - Nitroglycerin
  - Terbutaline

Pharmacist Learning Objectives
- Define vesicant, vesicant-like, irritant, and non-vesicant and their unique management when extravasated.
- Recognize risk factors for extravasation including iatrogenic causes, patient factors, and high-risk agents.
- Recall the pharmacology of agents used in the treatment of extravasation reversal.
- Construct an appropriate treatment regimen including both pharmacologic and non-pharmacologic options for the management of vesicant extravasation.
- Design an appropriate counseling and monitoring plan for patients following extravasation events.

Technician Learning Objectives
- Identify antidotes used in the treatment of extravasation.
- Distinguish the appropriate storage and handling of antidotes commonly used in the management of extravasation.
- Recognize the proper compounding technique and appropriate dispensing of medications utilized in the management of various extravasation events.

Extravasation
Efflux of solutions from a vessel or direct infiltration into the surrounding tissues during intravenous infusion
Incidence and Outcomes

- Extravasation of cytotoxic agents occurs at a rate of 0.01-6.5% 
  - Incidence of non-cytotoxic agent extravasation is largely unknown

- Majority occur in peripheral intravenous catheters (PIV)
  - Less common with central venous catheters (CVC)

- Lesions may continue to expand and typically heal slowly
  - Ulceration may require plastic surgery or skin-grafts
  - Superimposed infection may occur
  - Pain may persist for up to 1-2 weeks after extravasation

Classification of agents

- **Vesicant** – capable of producing edema, pain, erythema, and potentially tissue ischemia and blistering
- **Vesicant-like** – usually classified as irritants but may cause local blistering, pain, and potential necrosis
- **Irritant** – transitory effect characterized by burning sensation, pain, and redness during the infusion or extravasation
- **Non-irritant** – no local reactions, potentially mild inflammation or sensation of discomfort

### Classification of agents

<table>
<thead>
<tr>
<th>Vesicants</th>
<th>Vesicant-like</th>
<th>Irritants</th>
<th>Non-veiscants</th>
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<tbody>
<tr>
<td>Acrylates</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Dextranoyl</td>
<td>Anions</td>
<td>Antibiotics</td>
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<tr>
<td>Antimetabolites</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
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<tr>
<td>Anti-Myeloma</td>
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<td>Anti-mitotic</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Iodine</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Interferons</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Liposomal anthracyclines</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Cytotoxic agents</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Adrenergic</td>
<td>Anions</td>
<td>Antibiotics</td>
</tr>
</tbody>
</table>

**Vesicants**

- Docetaxel
- Liposomal doxorubicin
- Liposomal daunorubicin
- Gemcitabine
- Paclitaxel
- Topotecan
- Irinotecan

**Vesicant-like**

- Cisplatin
- Oxaliplatin
- Carboplatin
- Cytarabine
- Cladribine
- Fludarabine
- Fluorouracil
- Methotrexate
- Cytotoxic agents
- Vinca alkaloids
- Monoclonal antibodies
- Anthracyclines
- Topoisomerase inhibitors
- Alkylating agents

**Irritants**

- Sodium bicarbonate
- Calcium chloride
- Sodium chloride
- Glucose
- Dextrose
- Dextranoyl
- Hyaluronic acid
- Carboplatin
- Methotrexate
- Busulfan
- Carmustine
- Melphalan
- Ifosfamide
- Nafcillin
- Vancomycin
- Amphotericin
- Metronidazole
- Ganciclovir
- Vancomycin

**Non-veiscants**

- Calcium chloride
- Sodium bicarbonate
- Sodium chloride
- Dextranoyl
- Hyaluronic acid
- Carboplatin
- Methotrexate
- Busulfan
- Carmustine
- Melphalan
- Ifosfamide
- Nafcillin
- Vancomycin
- Amphotericin
- Metronidazole
- Ganciclovir
- Vancomycin
Asparaginase
Monoclonal Antibodies
Interferon
Antibiotics
Antimetabolites
Non-vesicants


Risk Factors

<table>
<thead>
<tr>
<th>Patient Specific Factors</th>
<th>Iatrogenic Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile, small, or mobile veins</td>
<td>Inexperienced personnel</td>
</tr>
<tr>
<td>Sclerosed veins</td>
<td>Multiple attempts at cannulation</td>
</tr>
<tr>
<td>Multiple courses of intravenous therapy</td>
<td>Cannulation at an unsuitable site</td>
</tr>
<tr>
<td>Obesity</td>
<td>Infusion pumps</td>
</tr>
<tr>
<td>Impaired or altered circulation</td>
<td>Improper cannulation</td>
</tr>
<tr>
<td>Difficulty with communication</td>
<td>Prolonged infusion</td>
</tr>
<tr>
<td>Medication side effects</td>
<td>Pressure bag use</td>
</tr>
</tbody>
</table>

Preventing extravasation

- Medical, pharmacy, and nursing team education and coordination
- Appropriate vascular access
- Appropriate cannula and needle selection
- Institution guidelines for extravasation

Preventing extravasation

- Patient Education
  - Risk of extravasation
  - Accurate history of previous extremity manipulation
  - Report discomfort, pain, redness or swelling immediately
  - Understand risk associated with PIV versus CVC

Preventing extravasation

- Proper administration of vesicant drugs
  - Use central line when possible
  - Recent placement of line
  - Avoid dorsum of hand or near joints
  - Do not cover cannula entry site
  - Do not test with cytotoxic drug
  - Flush line every 2-3 minutes

Diagnosis of Extravasation

- Patient symptoms
  - Tingling, burning, discomfort, pain, swelling or redness

- Nursing staff education
  - Frequently monitoring for swelling, redness, blanching, absence of blood return, or resistance during bolus administration

- Differential Diagnosis

<table>
<thead>
<tr>
<th>Local side reactions</th>
<th>Chemical plethysms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase</td>
<td>Diethylcarbamazine</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Melphalan</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>S-IVU</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Vinorelbine</td>
</tr>
</tbody>
</table>

Preventing extravasation

Image: https://shutr.bz/2nYEhyp


### Management Principles of Extravasation

- Immediate Management
- General Management
- Specific Management

### Immediate Management of Peripheral IV Extravasation

1. **STOP** the infusion AND **DISCONNECT** the infusion set
2. **LEAVE** the needle in place and **ASPIRATE** as much fluid as possible
3. **DO NOT** remove needle for cisplatin ≥ 0.4 mg/mL or bendamustine

### Immediate Management of Central IV Extravasation

1. **STOP** the infusion AND **DISCONNECT** the infusion set
2. **LEAVE** the central line in place and **ASPIRATE** extravasated fluid
3. **URGENT** Chest X-ray or thoracic computed topography (CT) imaging and **CONSULT** surgery

### General Management

1. **MONITOR** every 5-10 minutes for altered mental status and any significant skin changes
2. **APPLY DRY** compresses for 15 minutes every 6 hours

### Images

- [Image 1](https://bit.ly/2nYPK0)
- [Image 2](https://bit.ly/1T9Llil)
- [Image 3](https://bit.ly/374kYiz)
- [Image 4](https://bit.ly/3psB8Dp)
- [Image 5](https://bit.ly/3psB8Dp)
**General Management – Documentation**

- **Patient Name and MRN**
- **Date and Time Extravasation**
- **Name of Drug and Diluent**
- **Description of Intravenous Access**
- **Amount of Drug Extravasated**
- **Location and Size of Extravasation**

**General Management – Documentation**

- **Erythema, Swelling, and Induration**
- **Presence or Absence of Pain**
- **Record Pain Management Steps**
- **Other Agents Administered**
- **Include Photographs if Possible**
- **Continue to Document Progression**

**Pharmacology Specific Management**

1. Vasoconstriction/Ischemic Necrosis
2. Direct Toxicity
3. Osmotic Damage
4. Extrinsic Mechanical Compression

**Extravasation of Sympathomimetic Agents**

- **Mechanism**: Local stimulation of α-adrenergic receptors may lead to tissue ischemia
- **Agents**: Dobutamine, Dopamine, Epinephrine, Norepinephrine, and Phenylephrine
- **Specific Management**: Warm compress, Phentolamine, Terbutaline, and Nitroglycerin Ointment

**Extravasation of Sympathomimetic Agents**

- **Age < 2 years old**: Nitroglycerin ointment
- **Age ≥ 2 years old**: Phentolamine

**Antidotes for Sympathomimetic Agents - Phentolamine**

- Non-specific α-receptor antagonist, competes with catecholamines to reverse ischemia
- **Phentolamine**
- α2 receptor
- α1 receptor

Use terbutaline/nitroglycerin only when an shortage or contraindicated.
Antidotes for Sympathomimetic Agents - Terbutaline

**Adults**: 5-10 mg subcutaneously in multiple small injections
Children: 0.1-0.2 mg/kg subcutaneously (5 mg max)

Prepare by diluting 1 mL of terbutaline solution in 10 mL of sodium chloride 0.9%

Administer as soon as possible but within 12 hours
Repeat assessment of distal circulation at site

Antidotes for Sympathomimetic Agents - Terbutaline

Selective β₂-receptor agonist, vasodilatory effect attenuates vasoconstriction

**Extravasation of Highly Acidic/Alkali Agents**

**Mechanism**

Exposure to alkaline or acidic solutions (pH <5 or >9) causes tissue damage

**Agents**

See pH specific table

**Specific Management**

Warm dry compress and avoid neutralization

Acidic and Basic Agents

<table>
<thead>
<tr>
<th>pH ≤ 3</th>
<th>pH 3-5</th>
<th>pH 5-7</th>
<th>pH ≥ 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Amsulodine</td>
<td>Amphotericin</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Gentamicin</td>
<td>Ceftriaxone</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Cefepime</td>
<td>Dexamethasone</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Cefazolin</td>
<td>Labetalol</td>
<td>Aztreonam</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Captopril</td>
<td>Lorazepam</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Diazepam</td>
<td>Metoprolol</td>
<td>Furazolidone</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Propranolol</td>
<td>Metronidazole</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Metoclopramide</td>
<td>Nafldamins</td>
<td>Ganciclovir</td>
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**Terbutaline**

Selective β₂-receptor agonist, vasodilatory effect attenuates vasoconstriction

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Prepare by diluting 1 mL of terbutaline solution in 10 mL of sodium chloride 0.9%

Administer as soon as possible but within 12 hours
Repeat assessment of distal circulation at site
Extravasation of Hyperosmolar Solutions

**Mechanism**
Exert osmotic pressure and cause a shift of intracellular fluid into interstitial space

**Agents**
TPN, see hyperosmolar agents table

**Specific Management**
Cold compress, hyaluronidase, and potential fasciotomy

Hyperosmolar Agents

<table>
<thead>
<tr>
<th>≥ 290-500 mOsm/kg</th>
<th>≥ 501 mOsm/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Lipids</td>
<td>Dextrose ≥ 10%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Calcium Chloride 10%</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Sodium Bicarbonate ≥ 8.4 mEq</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Potassium Chloride ≥ 2 mEq/mL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Sodium Chloride ≥ 3%</td>
</tr>
</tbody>
</table>

What if my extravasated drug is acidic and hyperosmolar?

Vancomycin
pH 2.5-4.5
~350 mOsm/kg

What if my extravasated drug is alkali and hyperosmolar?

Phenytoin
pH 12
Conc. Dependent

Antidote for Hyperosmolar and Vinca Alkaloids - Hyaluronidase

Modifies permeability of connective tissue increasing distribution and absorption

Extravasation of Vinca alkaloids

**Mechanism**
Direct cellular damage, may have delayed erythema but intense pain

**Agents**
Vinblastine, vincristine, and vinorelbine

**Specific Management**
Warm compress, Hyaluronidase
**Antidote for Hyperosmolar and Vinca Alkaloids - Hyaluronidase**

**Adult:** 150 units/mL in 5 separate 0.2 mL subcutaneous injections

**Pediatric:** 15 units/mL in 5 separate 0.2 mL subcutaneous injections

Subcutaneous – Administer at leading edge of extravasation site

Be careful of product used, preparation instructions differ

Administer as soon as possible within 60 minutes

Vinca alkaloids use 1 mL for each 1 mL of extravasated drug

**Extravasation of Anthracyclines and Mitoxantrone**

**Mechanism**

Cellular uptake causes continuous cycles of tissue damage

**Agents**

Daunorubicin, Doxorubicin, Idarubicin, Mitomycin, Mitoxantrone

**Specific Management**

Cold compresses, Dimethyl sulfoxide (DMSO) 99%

Use DMSO 99% only when extravasation is severe or contraindicated

**Antidote for Anthracycline Agents + Mitoxantrone - Dexrazoxane**

1. Binds topoisomerase II and prevents formation of free radicals
2. Binds free and bound iron to displace anthracycline-iron complexes and reduce oxidative stress to cardiac tissue

Day 1: 1000 mg/m² IV in 1000 mL NaCl 0.9% over 1-2 hours
Day 2: 1000 mg/m² IV in 1000 mL NaCl 0.9% over 1-2 hours
Day 3: 500 mg/m² IV in 1000 mL NaCl 0.9% over 1-2 hours

Give ASAP but within 6 hours of extravasation in opposite arm from extravasation

Remove compress 15 min before and after completing the infusion

Reduce dose by 50% if CrCl < 40 mL/min

**Antidote for Anthracycline Agents + Mitoxantrone – Dimethyl Sulfoxide (DMSO) 99%**

1. Increases permeability of tissue by vasodilation
2. Neutralizes free radicals

Adult/Pediatric: Apply DMSO 99% topically, covering twice the affected area every 6 hours for 14 days

Give ASAP but within 10 minutes of extravasation

Saturate swab prior to application and do NOT use occlusive dressing

May cause local irritation, redness, sensation of heat and garlic breath

**Extravasation of (some) Alkylating Agents**

**Mechanism**

Leads to direct tissue damage through the cross linking of double stranded DNA

**Agents**

Cisplatin (≥ 0.4 mg/mL) and Bendamustine

**Specific Management**

Cold compress, Sodium thiosulfate
**Antidote for Cisplatin and Bendamustine - Sodium Thiosulfate**

- Prevents tissue damage by providing a substrate for alkylation in subcutaneous tissue
- Inject 2 mL of 1/6 molar solution, for every 100 mg of cisplatin extravasated
- Inject 2 mL for every 1 mg of bendamustine extravasated
- Administer ASAP or within 1 hour of extravasation
- Preparation varies dependent on concentration of solution
- Keep catheter in place to administer; may administer subcutaneously

**Preparation of Antidotes – Sodium Thiosulfate**

- **Preparation Differs by Concentration**
  - **10%**
    - 1/6 molar = 4 mL solution + 6 mL SWFI
  - **25%**
    - 1/6 molar = 1.6 mL solution + 8.4 mL SWFI

**Extravasation of Oxaliplatin**

- **Mechanism**
  - Longer duration of DNA inhibition which may lead to prolonged vesicant potential
- **Agents**
  - Oxaliplatin
- **Specific Management**
  - Warm compress, Dexamethasone 8 mg IV or PO twice daily for up to 14 days

**Extravasation of Other Anti-Neoplastics**

- **Mechanism**
  - May lead to erythema, tenderness, and swelling
- **Agents**
  - Docetaxel, Paclitaxel, Cabazitaxel, Ado-trastuzumab, etc.
- **Specific Management**
  - Cold compress, no specific antidote

**Follow-Up Management**

- Maintain communication in the outpatient setting
- Plastic surgery consult if continuing symptoms
- Counsel patient on use of extremity after symptoms resolve
- Counsel patient on specific antidote instructions and wound care

**Additional Interventions**

- **Saline flush out**
- **Surgical debridement**
- **Hyperbaric oxygen therapy**
  - Squeeze technique
- **Liposuction**
Storage of Antidotes

- **Naloxone**
  - Vasopressors administered
  - Various sizes of 2% topical ointment
  - Room temperature

- **Phentolamine**
  - Pharmacy/Vasopressors administered
  - Reconstituted with 1 mL of sterile water
  - Room temperature

- **Terbutaline**
  - Pharmacy/Vasopressors administered
  - Remember to dilute further
  - Room temperature

- **Dexrazoxane**
  - Pharmacy storage only
  - Multiple strength vials available
  - Room temperature

- **Sodium Thiosulfate**
  - Pharmacy/Oncology units
  - Multiple strength vials available
  - Room temperature

- **DMSO 99%**
  - Pharmacy storage
  - Only reagent grade chemical available from biochemical supplier
  - Room temperature

**Patient Case**

KP is a 79 y.o. male with anaplastic T cell lymphoma admitted for right upper extremity (RUE) cellulitis after Stage 3 extravasation of chemotherapy while receiving his first cycle of BV-CHP (brentuximab, cyclophosphamide, doxorubicin, and prednisone) therapy.

PMH: PAD, depression, hearing loss, acid reflux, anxiety and Crohn’s disease

Nurse noted at the time of discharge from clinic RUE bulging near PIV site. Patient went to the bathroom while Brentuximab was infusing and likely extravasated at this time. Although unsure which agent extravasated.

Five days later KP presents with increased redness, swelling, and blistering despite elevating and icing the site four times daily. Per plastic surgery consult the patient was started on intravenous antibiotics (cefepime and vancomycin) due to concern for cellulitis.

**Question #1**

Which agent in KP’s treatment regimen is classified as a vesicant?

A. Brentuximab  
B. Doxorubicin  
C. Cyclophosphamide  
D. Prednisone

**Question #2**

Which of the following are considered risk factors for KP to extravasate?

A. Small, fragile, or mobile veins  
B. Prolonged infusions (≥30 minutes or continuous)  
C. Impaired circulation  
D. Communication difficulty  
E. Multiple courses of intravenous therapy  
F. All of the above
**Question #3**

Please match the extravasated agent to its appropriate pharmacologic management.

<table>
<thead>
<tr>
<th>Extravasated Agents</th>
<th>Pharmacologic Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Sodium thiosulfate</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Hyaluronidase</td>
</tr>
<tr>
<td>Potassium</td>
<td>Dexrazoxane</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>No Specific Antidote</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
</tr>
</tbody>
</table>

**Question #4**

List in order the appropriate steps for the management of KP's extravasation (assume doxorubicin was the most likely agent).

A. Withdraw blood to remove extravasated drug.
B. Administer dexrazoxane.
C. Apply dry cold compresses for 15 minutes every 6 hours.
D. Remove infusion catheter or needle.
E. Inform provider of extravasation.
F. Delineate the affected area with a marker on the patient’s skin.
G. Stop the infusion.

**Question #5**

Describe the mechanism of action of dexrazoxane?

I. Binds topoisomerase II and prevents the formation of free radicals
II. Modifies permeability of connective tissue increasing distribution and absorption
III. Binds free and bound iron to displace anthracycline-iron complexes and reduce oxidative stress to cardiac tissue

A. I & II
B. I & III
C. All of the above

**Question #6**

What is the appropriate storage of each antidote?

A. DMSO 99% – Room Temperature
B. Dexrazoxane – Room Temperature
C. Sodium Thiosulfate – Room Temperature
D. Phentolamine – Room Temperature
E. Hyaluronidase – Refrigerator
F. All of the above