Management of Extravasation Injuries: A Focused Evaluation of Noncytotoxic Medications

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Extravasations are common manifestations of iatrogenic injury that occur in patients requiring intravenous delivery of known vesicants. These injuries can contribute substantially to patient morbidity, cost of therapy, and length of stay. Many different mechanisms are behind the tissue damage during extravasation injuries. In general, extravasations consist of four different subtypes of tissue injury: vasoconstriction, osmotic, pH related, and cytotoxic. Recognition of high-risk patients, appropriate cannulation technique, and monitoring of higher risk materials remain the standard of care for the prevention of extravasation injury. Prompt interdisciplinary action is often necessary for the treatment of extravasation injuries. Knowledge of the mechanism of extravasation-induced tissue injury, agents for reversal, and appropriate nonpharmacologic treatment methods is essential. The best therapeutic agent for treatment of vasopressor extravasation is intradermal phentolamine. Topical vasodilators and intradermal terbutaline may provide relief. Intradermal hyaluronidase has been effective for hyperosmotic extravasations, although its use largely depends on the risk of tissue injury and the severity of extravasation. Among the hyperosmotic agents, calcium extravasation is distinctive because it may present as an acute tissue injury or may possess delayed clinical manifestations. Extravasation of acidic or basic materials can produce significant tissue damage. Phenytoin is the prototypical basic drug that causes a clinical manifestation known as purple glove syndrome (PGS). This syndrome is largely managed through preventive and conservative treatment measures. Promethazine is acidic and can cause a devastating extravasation, particularly if administered inadvertently through the arteriolar route. Systemic heparin therapy remains the accepted treatment option for intraarteriolar administration of promethazine. Overall, the evidence for managing extravasations due to noncytotoxic medications is nonexistent or limited to case reports. More research is needed to improve knowledge of patient risk, prompt recognition of the extravasation, and time course for tissue injury, and to develop prevention and treatment strategies for extravasation injuries.

Key Words: iatrogenic injury, emergency treatment, infiltration, tissue necrosis, compartment syndrome, vasopressors, hyperosmolar therapy, hypoosmolar therapy, acidic and alkaline agents, phentolamine, hyaluronidase, terbutaline, nitroglycerin, radiographic contrast, calcium.


Extravasation injuries are a major cause of iatrogenic morbidity to the hospitalized patient.

The incidence of extravasation injury depends on both the patient and the medication, with nonvesicant extravasations occurring in 0.1–6% of adult patients and up to 11% of pediatric patients.1,2 Fortunately, most of these injuries can be prevented with appropriate cannulation techniques and preventive precautions. If an extravasation does occur, prompt recognition and timely, appropriate treatment may prevent further tissue injury, pain, or even limb loss.
However, unrecognized extravasations remain a cause of serious liability for the clinician, with lawsuits for mismanaged cases averaging $66,000 per litigation. As many as 25% of extravasation injuries cause a burden of disease more severe than the patient’s principal admitting diagnosis, including: pain, limitations in mobility, decreased function, permanent nerve damage, soft tissue sloughing, tendon damage, loss of limb function, and mortality. The primary approach to an extravasation injury includes a combination of nonpharmacologic efforts to delay further tissue damage, a reversal agent specific to the type of extravasation, and surgical intervention, if necessary. Although there is a reasonable availability of antidotes for extravasation injuries, only a minority of patients with these injuries receive an available antidote. In a retrospective study of 42 documented pediatric extravasations, only 33% of patients received an appropriate antidote, although 81% of patients qualified for treatment. Specific guidelines are available for radiographic contrast and chemotherapy extravasations, but comprehensive evidence-based management recommendations for each specific extravasation are lacking. Thus, our main purpose was to evaluate the primary literature for available interventions for the management of extravasations and to provide recommendations based on treatment literature for specific therapeutic modalities for noncytotoxic medications. Additionally, the pathophysiologic mechanisms for tissue injury and common patient presentations are described to assist the clinician in appropriate extravasation identification and to provide the rationale for available treatment strategies.

Definitions, Classifications of Injury, and Risk Factors for Extravasation

The definitions for extravasation and infiltration vary and are often deemed interchangeable. Extravasation is defined as the inadvertent extravascular administration of a medication or solution that has the potential for severe tissue or cellular damage into the surrounding tissue. Conversely, infiltration is defined as the inadvertent extravenous administration of any nonvesicant solution. Infiltrations may or may not cause a degree of local tissue inflammation or discomfort to the patient. For the purpose of this review, the definitions just stated were used for the basis of differentiating the need for urgent intervention. These definitions should be considered with caution, however, because untreated infiltrations can still cause severe pain, discomfort, or compartment syndrome if left untreated for an extended period of time.

Several staging systems have been derived for the classification of infiltrations. The degree of pain, extent of swelling, presence of blanching, and extent of circulatory impairment are incorporated into most of these classification systems (Table 1). Revised scales for pediatric and neonatal infiltrations have also been created to account for the smaller surface area and distinctive presentations of injury.

The etiology of extravasation and infiltration injuries can be separated into two different categories: mechanical and pharmacologic. Mechanical contributions to extravasation injuries largely involve cannulation technique or a patient’s physiologic predisposition to infiltration injury. Cannulation practices contributing to extravasation injury include inadvertent
puncture of a vein proximal to the site of injury, use of unstable catheters, use of a catheter larger than the vein size, use of a site near joint flexion, and catheter malfunction. Use of a metal catheter can double the risk of infiltration compared with a polyethylene catheter because puncture of the proximal vein wall is more likely. Multiple patient-specific risk factors have been identified in case series and retrospective reviews (Table 2). Most extravasations occur as a result of backflow of the substance from the catheter tip through the initial venous puncture site or site of cannulation. This is commonly caused by distal obstruction, which may be attributed to venous inflammation, clotting, or vasoconstriction. Patients with vasculopathies, lymphedema, and peripheral vascular disease may be predisposed to infiltration through this process. Patients may be at higher risk for extravasation due to multiple access attempts distal to the initial access attempt that may produce leakage of material along the punctured vein. Inflammatory edema and accumulation of fluid in the intradermal space can cause ischemic damage as arteriolar compression ensues, compromising the tissue blood supply. Patients may have variation in their radial or ulnar artery anatomy, leading to superficial distribution and subsequent intraarterial administration of an intravenous substance.

The physiochemical properties of an infiltrated substance will largely determine the propensity for tissue damage after the fluid has infiltrated. However, some agents may contribute to the mechanism of extravasation itself through direct venous damage, inflammation-induced vasoconstriction, or direct vasoconstriction. The pharmacologic causes of extravasation can be divided into several major categories based on the physiochemical properties of the causative agents. These include osmotically active solutions, vasoconstrictive substances, cytotoxic agents, and substances with a nonphysiologic pH. Regardless of the causative agent, nonpharmacologic interventions are a critical first step for the management of any extravasation (Table 3). Commonly reported agents within each class are listed in Table 4 with their respective mechanisms of injury and recommended treatment options. For the extent of this review, each of these categories is covered in detail with descriptions of common clinical syndromes, mechanisms of injury, antidotes studied, and common offending agents within each extravasation class. Cytotoxic extravasations are beyond the scope of this review, and their management has been extensively reviewed elsewhere.

### Table 1. Grading of Infiltration and Extravasation Injuries by Clinical Severity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical criteria</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Blanched skin</td>
</tr>
<tr>
<td></td>
<td>Edema &lt; 1 inch (2.54 cm) in any direction</td>
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<tr>
<td></td>
<td>Cool to touch</td>
</tr>
<tr>
<td></td>
<td>With or without pain</td>
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<tr>
<td>2</td>
<td>Blanched skin</td>
</tr>
<tr>
<td></td>
<td>Edema 1–6 inches (2.54–15.24 cm) in any direction</td>
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<tr>
<td></td>
<td>Cool to touch</td>
</tr>
<tr>
<td></td>
<td>With or without pain</td>
</tr>
<tr>
<td>3</td>
<td>Blanched, translucent skin</td>
</tr>
<tr>
<td></td>
<td>Gross edema &gt; 6 inches (15.24 cm) in any direction</td>
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<tr>
<td></td>
<td>Cool to touch</td>
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<tr>
<td></td>
<td>Mild to moderate pain</td>
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<tr>
<td></td>
<td>Possible numbness</td>
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<tr>
<td>4b</td>
<td>Blanched, translucent skin</td>
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<tr>
<td></td>
<td>Tight, leaking skin</td>
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<tr>
<td></td>
<td>Discolored, bruised, swollen skin</td>
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<tr>
<td></td>
<td>Gross edema &gt; 6 inches (15.24 cm) in any direction</td>
</tr>
<tr>
<td></td>
<td>Deep pitting edema</td>
</tr>
<tr>
<td></td>
<td>Circulatory impairment present</td>
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<td></td>
<td>Moderate to severe pain</td>
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</tbody>
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**Infiltration of any amount of irritant or vesicant**

*Grading should be assigned by the most severe clinical indicator of injury.*

*All extravasations should be graded as grade 4.*

### Vaspressors

Vasopressor infiltration leads to high intradermal concentrations of the vasopressor into the local tissue. As a result, direct α-adrenergic-mediated vasospasm of the smaller veins and the vasa vasorum ensues, leading to inadequate distal blood flow. Subsequent increases in the hydrostatic pressure of the venous circulation cause further effusion of the vasopressor into the tissues. Ischemia then follows parallel to the infusion site as the vasopressor diffuses into tissue space and the tributary veins constrict. As venous inflammation occurs, backflow commences into the arteriolar capillaries due to hydrostatic pressure. Sloughing has also been reported at the insertion site of longer peripheral catheters despite the maintenance of vein integrity. Risk factors for vasopressor necrosis include presence of vasculopathy, pre-existing hypotension, diabetic neuropathy, Raynaud disease, coagulopathy, advanced age, and altered mental status. Local venous anatomy remains an important variable as well, with higher frequencies of extravasation reported...
in areas with smaller veins or slower circulation such as the antecubital fossa of the wrist or the saphenous vein of the ankle.9, 10, 16, 18 Larger veins provide adequate dilution of the vasopressor and are less likely to spasm.9 Although the absolute rate of peripheral vasopressor-induced necrosis is unknown, the original rates of ulceration from the peripheral administration of norepinephrine were as high as 46–60%.19 Similarly, infiltration rates as high as 68% have been reported with the peripheral administration of dopamine in adults.20 More recent pediatric literature suggests that the rates of infiltration have been reduced to 15% with the use of modern venous access devices and larger peripheral veins.21 Regardless of the incidence of extravasation, the extended use of a vasopressor necessitates the eventual placement of central venous access.22

The clinical course of untreated extravasation remains fairly consistent across the vasopressors, although it can be difficult to predict whether an infiltration will remain asymptomatic or progress to florid necrosis.10 The site of infiltration typically manifests with blanching, swelling, hypoperfusion, and local hypothermia. This is followed by purple discoloration and extreme pain, and within 48 hours, fluid-filled bullae or vesicle formation.23 This may lead to skin epithelialization, tissue sloughing, eschar formation, or gangrene. The morbidity from vasopressor necrosis is often high, requiring aggressive tissue debridement, grafting, extremity amputation, or even mortality.

### Table 2. Etiologies of Extravasation by Risk Factor Category4, 13

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infusion-specific factors</strong></td>
<td>Duration of infusion&lt;br&gt;Infiltration volume&lt;br&gt;Catheter gauge (relative to vein size)&lt;br&gt;Inadequately secured catheter&lt;br&gt;Catheter type (steel &gt; Teflon &gt; polyurethane)&lt;br&gt;Infusion rate&lt;br&gt;Catheter location in elbow, ankle, dorsum of hand, or any other point of flexion&lt;br&gt;Multiple venous access attempts proximal to site of venous access&lt;br&gt;Need for catheter readjustments</td>
</tr>
<tr>
<td><strong>Patient-specific factors</strong></td>
<td>Patient skin color (darker skin may delay time to detection)&lt;br&gt;Hypotension8&lt;br&gt;Decompensated blood flowa&lt;br&gt;Peripheral vascular diseaseb&lt;br&gt;Raynaud diseasec&lt;br&gt;Prior extravasation injury&lt;br&gt;Altered skin and subcutaneous tissue integrity&lt;br&gt;Excessive patient movement around venous access site&lt;br&gt;Clot formation at cannulation site4&lt;br&gt;Lymphedema&lt;br&gt;Extremes in age (elderly, neonatal)e&lt;br&gt;Altered mental status or inability to verbalize painf&lt;br&gt;Peripheral neuropathy or other altered sensory perceptiong&lt;br&gt;Variation in venous and arteriolar anatomy</td>
</tr>
<tr>
<td><strong>Health care–specific factors</strong></td>
<td>Lack of knowledge of intravenous access establishment or access skills&lt;br&gt;Lack of knowledge of common vesicants&lt;br&gt;Distractions or lack of monitoring for infiltration during drug administration of high-risk drugs&lt;br&gt;Infiltration during overnight shift</td>
</tr>
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*Authors have speculated that the lack of adequate forward venous flow may allow accumulation in the local venous supply, resulting in vasospasm and infiltration into the surrounding tissue.*

*Earlier evidence suggested that patients with vasculopathies were at particularly higher risk for extravasations, secondary to venous stasis, and multiple attempts may be necessary for peripheral intravenous access.*

*It is believed that patients with Raynaud disease are particularly sensitive to adrenergically mediated vasospasm, which may be an early aspect of progression to infiltration and extravasation.*

*Many extravasations are a result of backflow, often caused by clotting at the tip of the vascular access device.*

*Advanced age is likely a combination of the patient-specific risk factors.*

*Inability to report the most important initial sign of extravasation, burning pain at the site of infiltration, may result in a more extensive progression of extravasation prior to detection by a health care provider. Also, patients with altered mentation may be pulling vascular access devices, resulting in inadvertent intradermal administration of a drug.*

*Lack of ability to feel initial infiltration may result in progression of injury prior to detection.*
For most medications, the treatment of extravasation includes the following steps:

1. Stop the intravenous push or infusion immediately if the patient admits to a burning sensation or complains of pain.
2. The catheter or needles should not be removed immediately but should be left in place to attempt aspiration of fluid from the extravasated area. Aspiration of the drug and surrounding fluid should be attempted with 3–5 ml of blood. If available, injection of reversal agents through the infiltrated catheter allows delivery to the same injured tissue plane.
3. Remove the needle.
4. Elevate the affected limb to minimize swelling and encourage lymphatic resorption of the drug.
5. Apply warm or cold compresses as indicated. This decision is usually based on physician preference and the type of drug extravasated. Cold compression may reduce subsequent inflammation and necrosis caused by most agents. In general, cold compression is recommended for extravasation of all vesicant or irritant drugs except for the vinca alkaloids (vincristine, vinblastine, vinorelbine), epipodophyllotoxins (etoposide), and vasopressors because cold worsens tissue ulceration caused by these drugs. Cold compresses should be applied for 20 min, 3 or 4 times/day, for the first 48–72 hrs after extravasation occurs. Hot compresses are sometimes preferred for specific drug extravasation (e.g., vinca alkaloids, phenytoin, vasopressors, contrast media) to modify viscosity, increase local blood flow, and enhance drug removal.
6. Debridement and excision of necrotic tissue should be considered if pain continues for 1–2 wks. Surgical flushing with normal saline is often used for severe hyperosmolar extravasations. Assessment and surgical decompression of compartment syndrome may be necessary in certain cases of extravasation.

Table 3. Nonpharmacologic Treatment Interventions for Extravasations

The recommended approach to the treatment of extravasation includes the following steps:

1. Stop the intravenous push or infusion immediately if the patient admits to a burning sensation or complains of pain.
2. The catheter or needles should not be removed immediately but should be left in place to attempt aspiration of fluid from the extravasated area. Aspiration of the drug and surrounding fluid should be attempted with 3–5 ml of blood. If available, injection of reversal agents through the infiltrated catheter allows delivery to the same injured tissue plane.
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*For most medications, the treatment of extravasation is nonpharmacologic; the efficacy of any specific approach has not been demonstrated in controlled studies.

Reported evidence supporting the treatment of extravasation caused by individual vasopressors is outlined in the following section. Most imperative, early treatment can prevent any necrotic complications from occurring. Nondrug therapy has an important role in the early management of vasopressor extravasation. The infusion of the drug should be stopped immediately, with attempts to remove as much of the infiltrated drug as possible from the catheter. The limb should be elevated, with application of heat proximal to the cannulation site, which may assist in further vasodilation. Cooling the area should be avoided because it may cause exacerbation of the vasoconstrictive effects of the vasopressor.

Norepinephrine

Case reports of severe tissue sloughing and necrosis were reported in the literature shortly after norepinephrine became widely available as early as 1949. Norepinephrine remains the most frequently reported vasopressor extravasation in the literature. Therefore, most of the extravasation and treatment literature on vasopressors focused on this agent. The agent’s predominant effects are on the α₁-adrenoreceptor that mediates vascular smooth muscle vasoconstriction. Although the agent possesses a degree of vasodilatory β₂-adrenoreceptor activity, α₁ activity is believed to predominate due to both higher relative concentrations of the vasopressor during extravasation and distribution of the α₁-receptors on smooth muscle. Phenolamine, originally studied for its use as an α-adrenoreceptor antagonist in disease states such as pheochromocytoma and Raynaud disease, has become the treatment of choice for vasopressor extravasation. It increases the median effective dose for vasospasm in the presence of sympathetic amines. Compared with nitroprusside and nitroglycerin, phenolamine may produce greater increases in capillary blood flow in adrenoreceptor-mediated vasoconstriction. Phenolamine should be injected multiple times with a fine hypodermic needle throughout the site of injury, discoloration, or stiffness (Table 4). It may be also administered through the infiltrated cannula, if still in place. Hypoperfusion of the area should resolve within 7–10 minutes of administration. Systemic administration of phenolamine has not been proven to be an effective treatment for extravasation. Redosing of phenolamine may be necessary if the lesion continues to progress or if initial attempts to reverse the vasospasm remain unsuccessful. Unfortunately, phenolamine has markedly diminished efficacy as time progresses from the initial extravasation event. In animal models, no beneficial effect was seen if the agent was injected 18 hours after injury. In humans, the longest reported time from injury to effective treatment of any vasopressor is 13 hours. After the patient has been injected with phenolamine, he or she should be monitored for manifestations of hypotension, hyperemia, and pain from reperfusion of the injured area. Other pharmacotherapies for norepinephrine extravasation have remained largely ineffective or are underreported. Hyaluronidase, an enzyme that facilitates the degradation of the extracellular matrix, should be
<table>
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<tr>
<th>Drug or substance</th>
<th>Mechanism of tissue damage</th>
<th>Suggested emergent treatment options</th>
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</thead>
<tbody>
<tr>
<td><strong>Vasopressors</strong></td>
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<tr>
<td>Prototypical agents:</td>
<td></td>
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</tr>
<tr>
<td>Norepinephrine (NE)⁹, 23, 24, 31</td>
<td>Local ischemia secondary to vasoconstriction of veins, capillaries, and vasa vasorum; altered tissue metabolism, and redistribution of blood flow; spread through tributary veins</td>
<td>Peripheral IV: Preferred (NE, EPI, DA, DBA, and PE): Phentolamine 5–10 mg in 10–20 ml NS. Inject multiple injections with hypodermic needle across symptomatic areas; acceptable to redose if patient remains symptomatic. Preferred (V and MB): Topical nitroglycerin 2% 1-inch strip applied to site of ischemia; may redose every 8 hrs as necessary. Alternatives and adjuncts: Heat proximal to site of injection, elevation. Topical nitroglycerin (all vasopressors) 2% 1-inch strip applied to site of ischemia; may redose every 8 hrs as necessary. Terbutaline (NE, EPI, DA, and DBA) 1 mg in 10 ml NS. Inject locally across symptomatic sites. Autoinjector ischemia (EPI): Preferred: Phentolamine 0.5–4.5 mg in 5 ml NS. Avoid overdilution or excessive administration due to fixed finger volume. Alternatives and adjuncts: Topical nitroglycerin. Terbutaline 0.5–1 mg in 1 ml NS. Local injection: use 1:1 dilution to conserve volume in finger. No treatment, watchful waiting. Agents to avoid: Hyaluronidase monotherapy, ice packs, conivaptan. Specific nonpharmacologic treatments: Use of warm compresses has been well studied; consider elevation of extravasated extremity.</td>
</tr>
<tr>
<td>Epinephrine (EPI)²⁷, 31, 35</td>
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<tr>
<td>Dopamine (DA)¹⁷, 28–31</td>
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<tr>
<td>Dobutamine (DBA)³¹, 32</td>
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<tr>
<td>Methylene blue (MB)³⁸, 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin (V)</td>
<td></td>
<td></td>
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<tr>
<td>Phenylephrine (PE)</td>
<td></td>
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<tr>
<td><strong>Hyper and hypoosmolar agents</strong></td>
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<td></td>
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<tr>
<td>Prototypical agents:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total parenteral nutrition⁴²–⁴⁸, 53, 54</td>
<td>All agents: Direct cellular damage due to osmotic shifts from cellular membrane, cell volume dysregulation, DNA damage, apoptosis, and inflammation. TPN: Addition of pH-altering amino acids and electrolytes may result in further tissue damage. Calcium: May induce tissue damage due to calcium-induced vasoconstriction; deep tissue damage may occur; late-onset calcifications may occur.</td>
<td>Peripheral hyper- or hypotonic extravasation, calcium salts (early): Preferred: Hyaluronidase 15–25 units intradermally to border of extravasated area over five injections; hyaluronidase may also be injected through the catheter that caused the infiltration. Consider surgical evaluation for all concentrated calcium extravasations. Delayed calcium extravasation (calcinosis cutis): Preferred: Close monitoring; most calcifications will spontaneously resolve. Alternative/severe manifestations: sodium thiosulfate 12.5 g IV over 30 min; may increase gradually to 25 g 3 times/week. Monitor for non-anion gap acidosis, hypocalcemia, severe nausea.</td>
</tr>
<tr>
<td>Calcium chloride 10% (2040 mOsm/L)⁴⁸, 55, 56, 59</td>
<td></td>
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<tr>
<td>Calcium gluconate (669 mOsm/L)⁶⁰, 55, 56, 59</td>
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### Table 4. (continued)

<table>
<thead>
<tr>
<th>Drug or substance</th>
<th>Mechanism of tissue damage</th>
<th>Suggested emergent treatment options</th>
</tr>
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<tbody>
<tr>
<td><strong>Hyper and hypoosmolar agents (Continued)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic contrast media&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Radiographic contrast media:</td>
</tr>
<tr>
<td>Other agents:</td>
<td></td>
<td>&lt;50 ml, low-osmolality contrast media extravasation: Careful monitoring recommended; pharmacologic treatment often unnecessary</td>
</tr>
<tr>
<td>Aminophylline (10 mOsm/L)</td>
<td></td>
<td>&gt;50 ml low-osmolality contrast media, any high-osmolality contrast media, precursors of severe tissue injury: Consider use of hyaluronidase; dose may vary depending on the size of the infiltration</td>
</tr>
<tr>
<td>Dextrose 10–50% (504–2520 mOsm/L)</td>
<td></td>
<td>Alternative and adjunctive therapy:</td>
</tr>
<tr>
<td>Mannitol 20% (1369 mOsm/L)</td>
<td></td>
<td>TPN: Topical nitroglycerin 2% 1-inch strip or nitroglycerin 5-mg patch over area of extravasation</td>
</tr>
<tr>
<td>Hypertonic saline (concentration dependent)&lt;sup&gt;y&lt;/sup&gt;</td>
<td></td>
<td>Specific nonpharmacologic treatments:</td>
</tr>
<tr>
<td>Naficillin (363 mOsm/L)</td>
<td></td>
<td>Consider the use of warm or cold compresses, elevation.</td>
</tr>
<tr>
<td>Potassium (60 mEq/L = 763 mOsm/L)</td>
<td></td>
<td>Consider aseptic surgical flushing of the extravasated area with normal saline</td>
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<tr>
<td>Arginine (950 mOsm/L)</td>
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<tr>
<td>Ampicillin (566 mOsm/L)</td>
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<tr>
<td>Sodium bicarbonate 8.4% (2000 mOsm/L)</td>
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<tr>
<td><strong>Substances containing propylene glycol (osmolarity varies):</strong></td>
<td></td>
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</tr>
<tr>
<td>Etomidate, lorazepam, diazepam, nitroglycerin, digoxin, phenytoin, phenobarbital</td>
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<td></td>
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<tr>
<td><strong>Acidic and alkaline agents</strong></td>
<td></td>
<td></td>
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<tr>
<td>Prototypical agents:</td>
<td></td>
<td>pH-related extravasation injuries (general): Dry heat and elevation; patients should be closely monitored for signs of coagulation and ischemia.</td>
</tr>
<tr>
<td>Phenytoin (pH 10–12, &gt; 700 mOsm/L)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Phenytion (purple glove syndrome): Dry heat and elevation; patients should be closely monitored for development of tissue sloughing or compartment syndrome.</td>
</tr>
<tr>
<td>Acyclovir (pH 11)</td>
<td></td>
<td>Refractory cases: Hyaluronidase 15 units intradermally along injection site and edematous area.</td>
</tr>
<tr>
<td>Promethazine (pH 4.0–5.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>Intraarterial extravasation of acidic or basic substances:</td>
</tr>
<tr>
<td>Sodium thiopental (pH 10–11)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Leave inadvertent intraarterial line in place for diagnostics.</td>
</tr>
<tr>
<td>Vancomycin (pH 4.0)</td>
<td></td>
<td>Systemic heparin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Doxycycline (pH 1.8–3.3)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>Stellate ganglion block</td>
</tr>
<tr>
<td>Conivaptan (pH 3.4–3.8)</td>
<td></td>
<td>Nonpharmacologic treatment:</td>
</tr>
<tr>
<td>Amiodarone (pH 3.5–4.5)</td>
<td></td>
<td>Dry heat and elevation remain treatment of choice for pH-related extravasations.</td>
</tr>
<tr>
<td>Pentamidine (pH 6.5)</td>
<td></td>
<td>Attempts at neutralization of extravasated acidic or basic compounds should be avoided due to gas formation and exothermic reactions.</td>
</tr>
</tbody>
</table>

Alkaline products: Liquefactive necrosis generated due to hydroxide ions; causes collagen destruction, vasocnstriction, apoptosis, and edema; deep tissue damage more likely

Acidic products: Hydrogen ion donation and reductive capacity of acid anion salt produces tissue damage; causes coagulative necrosis, cellular desiccation, eschar formation, vasocnstriction, and edema

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<sup>a</sup>Osmolarity varies on the basis of concentration, ionization, and dimerization of contrast media. For a complete listing of contrast osmolarity, refer to reference 15.

<sup>b</sup>Hyaluronidase is commonly diluted to a 1:10 ratio (0.1 ml reconstituted hyaluronidase, 0.9 ml normal saline). A series of five injections of 0.2 ml is then administered with a tuberculin syringe until all 15 units are given. Dosage is expressed in turbidity reducing units (TRUs). One TRU will allow the dispersion of volumes up to 50 ml from the subcutaneous compartment.

<sup>c</sup>In general, systemic heparin for intraarterial-induced tissue damage is titrated to similar therapeutic activated partial thromboplastin times as in the use of the drug for deep venous thrombosis or pulmonary embolism.

IV = intravenous; NS = normal saline; TPN = total parenteral nutrition.

This table is not a comprehensive listing of all agents that can cause injury and reflects the most commonly reported agents that have well-described treatments.
avoided because it may cause a further expansion of vasoconstriction. Papaverine and procaine have been attempted without success. Vasodilators such as nitroglycerin or nitroprusside have not been reported as treatment options for nor-epinephrine extravasation specifically, but they may be effective based on reports of their successful use with other vasopressors.

**Dopamine**

As a vasopressor, dopamine possesses both the unique ability to act as a direct agonist to multiple adrenoreceptors, as well as facilitate the release of norepinephrine from the presynaptic terminal. At higher concentrations of dopamine, such as in extravasation, the agent possesses potent \( \alpha_1 \)-adrenoreceptor activity that leads to vasospasm, even if the agent is used within the lower dose range. Although the treatment literature is more limited than that for norepinephrine, it suggests that management of dopamine extravasations remains largely similar to norepinephrine. Intradermal phentolamine at a similar dosage and administration has been reported as a successful treatment modality. However, there are more case reports of treatment failures with phentolamine, although the timing of reversal was unclear in these cases. Nitroglycerin has been attempted most often with dopamine extravasation injuries, although most of the treatment experience with this agent was derived from symmetrical peripheral ischemic skin lesions, a different manifestation of necrosis than extravasation. Research reported the successful use of nitroglycerin in four infants with dopamine extravasations. A 1-inch strip of topical nitroglycerin 2% or a weight-based dose (4 mm/kg) established reperfusion within minutes of application. Although the infants required redosing at 8-hour intervals, resolution of ischemia was noted in all four cases. Careful monitoring for hypotension should be conducted because these doses meet or exceed the topical dosing of nitroglycerin for angina in adults. Because the use of topical nitroglycerin in adults remains very limited, dosing should remain similar to the pediatric case reports and peripheral ischemic skin lesions (up to 1 inch of 2% nitroglycerin, or 15 mg). In light of recent shortages of phentolamine, the successful use of terbutaline, a vasodilatory \( \beta_2 \)-agonist, has been reported for the treatment of dopamine extravasations. A dilution of terbutaline 1 mg in 10 ml of normal saline was associated with rapid improvement in ischemia after a combined dopamine and dobutamine extravasation of the hand.

**Dobutamine**

Although known mostly for its chronotropic and inotropic properties as a \( \beta_1 \)-agonist, dobutamine has been reported to cause dermal necrosis on extravasation. The agent does possess a degree of partial \( \alpha \)-agonist activity, at around one fortieth the potency of norepinephrine. At high local tissue concentrations, the \( \alpha_1 \)-agonism from dobutamine may be responsible for the cases of extravasation necrosis reported. Treatment of dobutamine extravasations remains speculative because reports of successful treatment are few. Terbutaline, as mentioned previously, has been successful for the reversal of a mixed dopamine and dobutamine extravasation. Phenolamine and nitroglycerin remain reasonable treatment options for dobutamine extravasations.

**Epinephrine**

As a vasopressor, epinephrine exudes relatively nonselective activity on \( \beta_1 \)-, \( \beta_2 \)-, and \( \alpha_1 \)-adrenoreceptors. Most of the described infiltration events with epinephrine come from inadvertent injections of high concentration solutions, usually by autoinjector devices contained in anaphylaxis treatment kits. Initial concerns for the use of intradermal epinephrine for local anesthesia were generated from case reports of ischemia induced by injection of anesthetics-vasoconstrictor combination products into digital extremities. However, there have been large inconsistencies in these reports regarding the concentration of epinephrine used, the use of low pH anesthetics, and the extent of the infiltration. Poor digital block technique, such as the use of circumferential blockade, large-bore needles, application of hot soaks, and the use of epinephrine in patients with vasospastic conditions may predispose digital ischemia. In a prospective observational study, the prudent use of dilute (1:100,000 or lower) epinephrine was proven safe in more than 3100 injections into the finger.

To date, there have been 19 published works on the management of 59 patients who have inadvertently self-injected concentrated (1:1000 or higher) epinephrine into the fingers. None of these cases led to digital necrosis or gangrene, regardless of treatment method. Concentrated phentolamine, at a dose of 0.5–4.5 mg, was the most commonly reported reversal agent used.
Multiple infiltrations of phentolamine along the digital arteries or a digital blockade have both been effective for reversal. Twenty-three cases received no reversal without serious complications. Depending on the concentration of epinephrine injected, spontaneous resolution of hypoperfusion can be expected within 5–13 hours without treatment. Whether phentolamine should be used in autoinjector-induced digital ischemia has become a matter of debate. In light of the pain associated with prolonged ischemia-reperfusion and the possibility of prolonged sensory loss for up to 10 weeks after injury, phentolamine may be used in cases refractory to nonpharmacologic measures because it can provide reversal of ischemia within 30–60 minutes of infiltration. Terbutaline, at a 1:1 dilution to conserve volume in the finger, has also been moderately successful at doses of 0.5–1 mg, although one case required a rescue dosing with phentolamine. Phentolamine remains a valid treatment option for intravenous extravasation of epinephrine in the setting of shock or cardiac arrest.

Phenylephrine

Compared with the other vaspressors, phenylephrine is the most selective to the α1-adrenoceptor. To our knowledge, there are no published case reports of phenylephrine extravasations in the English literature. A recent submission to the U.S. Food and Drug Administration, however, extravasation injury was listed as a postmarketing adverse event by the submitting company. A French article described a case report of necrosis ensuing after administration of a phenylephrine infusion for septic shock. The report details unsuccessful treatment of the extravasation with lidocaine and hyaluronidase. Proper treatment of phenylephrine extravasation remains largely unknown, although phentolamine may be efficacious due to its α1-adrenergic antagonism.

Methylene Blue (Methylthioninium Chloride)

Methylene blue has experienced a recent renewal in interest for the treatment of refractory septic shock and methemoglobinemia. The agent has a distinctive mechanism of action in that it produces its effects through inhibition of the enzymes guanylyl cyclase, cyclic guanosine monophosphate (cGMP), and nitric oxide synthase, leading to both the inhibition of nitric oxide synthesis and its vasodilatory actions. Extravasation of methylene blue causes intense vasoconstriction. Furthermore, oxidation of methylene blue into deaminized oxide free radicals may cause independent cytotoxic cellular injury. Topical organic nitrates may be a therapeutic option for the reversal of methylene blue-induced vasospasm because they increase nitric oxide tone. Animal studies indicate that methylene blue may also produce a downstream release of norepinephrine through effects independent of its activity on cGMP. In animal models, adrenergic antagonists have been effective for reversal of methylene blue-induced contractions, suggesting that phentolamine may also play a role in the treatment of methylene blue extravasation injuries.

Vasopressin

Unlike the catecholamine vasopressors, vasopressin exhibits its smooth muscle vasoconstrictive effects through V1 receptor coupling, signaling inositol 1,4,5-trisphosphate–mediated vasoconstriction. Since its resurgence in use for the treatment of septic shock and hepatorenal syndrome, case reports have emerged of extravasation and skin necrosis due to vasopressin. As a result of these reports, the authors of the Surviving Sepsis Campaign have revised their vasopressin recommendations to administer the drug through a central line. To date, no published reports have detailed the successful management of vasopressin extravasations. Although intravenous vasopressin antagonists exist, such as conivaptan, these agents should not be used until they are further studied for this indication. Conivaptan has a pH of 3.0 and is associated with high rates of phlebitis. Treatment with local nitroglycerin may be attempted because it often administered systemically for the prevention of the ischemic manifestations of high-dose vasopressin. Phentolamine or terbutaline may be useful but only on the basis of their intrinsic ability to induce vasodilation, as opposed to direct antagonism of vasopressin’s pharmacologic effects.

Osmotically Active Agents

There are few, if any, reports in the literature of extravasation injuries due to hypotonic agents; however, hyperosmolar agents pose a major risk for the devolvement of phlebitis and extravasation injuries. Exposure of cells to a
hypertonic substance causes a direct fluid shift from the intracellular space to the extracellular space. Osmotic stress leads to dysfunction in cellular transport, cell volume dysregulation, direct protein and DNA damage, formation of reactive oxygen species, and the induction of apoptosis. Most of the data for the upper tolerances of the peripheral venous system to an osmolar load is derived from the parenteral nutrition literature, which suggests that peripheral venous tolerance of total parenteral nutrition (TPN) does not exceed 900 mOsm/L.41 The ability of the venous system to tolerate osmolar loads depends on a variety of factors including catheter size, venous blood flow rate, duration of infusion, presence of the sheltering effect of intravenous lipids, and the infusion rate of the solution. In consideration of these factors, tolerance to osmolar loads in the peripheral vein may be as low as 600 mOsm/L or as high as 1200–1700 mOsm/L.41 This does not preclude the potential for tissue damage due to extravasation because they are not as rapidly removed from the tissues by the venous system. In consideration of these factors, substances as low as 650 mOsm/L may cause intense tissue inflammation and tissue damage on extravasation.42

Extravasation of extensively hyperosmolar substances may produce an osmotic draw into the fixed tissue compartment around the infiltration.43, 44 Even relatively isomolar substances may produce similar sequelae if the infiltration is left unmanaged. The presence of excess fluid in these fixed tissue compartments produces a vicious cycle of hypoperfusion, ischemia, and further edema as necrosis progresses.44 Patients should be monitored for the “six Ps” of compartment syndrome—pain, pallor, paresthesias, pulselessness, pressure, and paralysis—or a raised compartment pressure (higher than 30 mm Hg) after extravasation of hyperosmolar substances.45 Surgical evaluation for vascular compromise or compartment syndrome should be instituted in higher risk extravasations including the use of higher osmolality agents (higher than 1000 mOsm/L), patients with early symptoms, skin discoloration, or high-volume infiltrations.6 If compartment syndrome is diagnosed, emergent surgical decompression may be necessary to avoid compromise of tissue and nerve structures.

Nonpharmacologic treatment options may play an important role in the management of hyperosmolar extravasations. Similar to vasoactive agents, the infusion should be stopped immediately, with attempts to remove as much of the infiltrated drug as possible. Heat or cold compresses have both been studied (see further details in contrast media and calcium sections) as therapeutic options. Caution is warranted with the aggressive use of moist heat because it may lead to maceration and sloughing of the skin. Elevation may also be attempted to promote fluid removal into the capillaries, although evidence for the technique remains poor.46 Aggressive surgical flushing of the extravasated area with normal saline may assist with the removal of extravasated material, sparing tissue damage.47

The recombinant enzyme hyaluronidase has emerged as a commonly used treatment modality for hyperosmolar extravasations. The enzyme causes depolymerization of acid polysaccharides such as hyaluronic acid and chondroitin sulfates, resulting in a temporary dissolution of the interstitial barrier. This causes an increase in the distribution (three to fivefold) and absorption of intradermally injected substances, which has generated interest in its use for extravasation injuries. Hyaluronidase has been successfully used in the treatment of extravasated substances such as 10–50% dextrose, TPN, calcium, radiographic contrast media, potassium, mannitol, aminophylline, and nafcillin (Table 4).42, 48–50 Animal data have also found tissue-sparing effects during hypertonic saline infiltrations.51 Swelling may resolve as quickly as 15–30 minutes after administration of hyaluronidase. It may also be injected through the infiltrated catheter, allowing delivery of the enzyme along the injured tissue plane. Hyaluronidase is most efficacious in areas with lower subcutaneous fat content. Elderly patients may be less responsive to the effects of this agent due to inelastic skin.52 Patients receiving large doses of salicylates, corticosteroids, estrogens, or antihistamines may require larger doses of hyaluronidase because these agents may contribute to resistance to the enzyme.52 Purification of the enzyme has reduced the occurrence of allergic reactions to less than 1%.52 A test dose of hyaluronidase may be given, but a delay of more than 1 hour from extravasation to hyaluronidase treatment may negate any potential benefits of the enzyme. The enzyme should not be injected near active infection, purulence, or cancerous areas in light of the potential for metastasis.48, 52

Total Parenteral Nutrition

Extravasation of TPN may result in direct injury to the exposed tissue. Initial presentation
of TPN extravagations can include pain, inflammation, and erythema. Extravasation severity can range from benign lipid masses to florid skin necrosis. Hyaluronidase has been successfully used in the treatment of TPN extravagations. In two cases of TPN extravasation, 25 units of hyaluronidase were injected intradermally around the inflamed area, resulting in clinical improvement within 6–12 hours. Hyaluronidase has also been successful in the management of neonatal TPN extravagations, in combination with aggressive saline flushing of the affected tissue. Nitroglycerin has also been attempted for the treatment of extravasation in a neonate receiving TPN, although tissue sloughing still occurred despite treatment.

Calcium Salts

The commonly used calcium salts, calcium gluconate and calcium chloride, possess osmolarities of 669 and 2040 mOsm/L, respectively. Laboratory studies suggest that the absolute calcium content may be the strongest predictor of tissue necrosis. This may be due to direct protein precipitate formation caused by the calcium salts and subsequent vasoconstriction. Calcium extravasations may present as an acute tissue injury or may possess delayed clinical manifestations.

Acute calcium extravasation injuries often vary in clinical presentation and severity. Patients will frequently present with erythema and papules proximal to the injection site, usually within a few hours to a day after the infiltration. Progression of injury varies because necrosis induced by the cationic agent can be deep; penetration may occur into underlying fascia and skeletal muscle layers. Eschar formation occurs within 48–72 hours of initial injury, although necrosis may take as long as a few weeks to develop.

Acute calcium extravagations have been successfully managed with hyaluronidase by the subcutaneous or intradermal route. Due to the penetrating nature of the calcium salts, hyaluronidase may be only effective if used within 60 minutes of calcium extravasation. In severe cases, resection may be the only therapeutic option that may limit the progression of injury.

Delayed calcium extravagations usually occur after minor extravagations of calcium products that may initially remain asymptomatic or undetected. On infiltration, exogenous calcium may lead to soft tissue calcification through the formation of hydroxyapatite. This is thought to be caused by the precipitation of the calcium salt with phosphorus or the deposition of calcium onto exposed collagen. Chemically, calcium chloride dissociates more extensively than calcium gluconate, posing a higher risk for precipitation, although the clinical phenomenon occurs with both salts. These precipitations often appear as an amorphous mass, subcutaneous plaque, or vascular calcification on radiographic imaging. Radiographic manifestations of delayed calcium extravagations are often referred to as iatrogenic calcinosis cutis. Clinically, these often manifest as erythematous, hardened subcutaneous masses or papules at or proximal to the infiltration. These nodules appear 2–3 weeks after the initial infiltration and may take several months to resolve spontaneously. Because of the delayed onset, radiographic calcinosis cutis may be misdiagnosed as vascular disease, cellulitis, or osteomyelitis. It most frequently occurs in neonates but may also occur in adults receiving repeated doses of calcium salts. In most of the cases, these lesions spontaneously resolve over several months through transepidermal elimination, removing the necessity for intervention. In cases of severely debilitating, unresolving, or limb-threatening calcinosis cutis, sodium thiosulfate may be offered as treatment. Treatment experience with this drug is limited to a single pediatric case report and experience with the drug in the management of renal calciphylaxis. Calcium thiosulfate salts have high solubilities, allowing for the dissolution of precipitated calcium products. Sodium thiosulfate is most commonly dosed as 12.5–25 g intravenously over 30 minutes 3 times/week, with titration based on gastrointestinal tolerability. Patients should be monitored for hypocalcemia, nausea, or the development of anion gap acidosis. Despite treatment, complete resolution may take several months of therapy.

Radiographic Contrast Media

Like other extravasation injuries, the ability of radiographic contrast media to produce extravasation injury largely depends on the volume of infiltrated contrast media and site of access. Studies and case reports have demonstrated that contrast media with osmolalities of 1025–1420 mOsm/kg of water possess the highest risk for extravasation injury. Higher osmolality magnetic resonance imaging contrast media may also pose high risks for tissue necrosis. The use of lower osmolality contrast media has emerged.
because it may reduce the risk of nephrotoxicity and aspiration injury compared with higher osmolality contrast media. These lower osmolality agents have also largely reduced the risk of serious extravasation injury. In a retrospective review of more than 69,000 nonionic contrast media injections (290–780 mOsm/kg), infiltra-
tonion rates occurred in as low as 0.7% of patients receiving contrast, with serious complications only occurring in one patient (0.2% of infiltra-
tions). Moderate ulceration can occur on larger (more than 150 ml) extravasations of low osmolality contrast media. Patients with contrast media infiltrations may experience pain on injection of the agent, swelling, edema, and ery-
chema. Severe clinical manifestations, such as blistering and ulcerations, are rare but may often be delayed due to the inflammatory response to the infiltration, peaking at 24–48 hours; hyperal-
giesia may extend several weeks after the initial extravasation event. Progressive pain, altered tissue perfusion, paresthesias, and blistering may predict a higher severity of injury. Whether to apply warm versus cold compresses to extravasa-
tion of nonionic, low osmolality contrast media remains an area of clinical debate. Extravasation has been managed successfully with warm com-
presses and elevation alone, despite relatively large extravasations and the presence of edema. Warm compresses and elevation may modify the viscosity of the infiltrated contrast, promote vasodilation, and encourage the removal of the contrast media into the circulation. Some insti-
tutions endorse the use of cold compresses because they may prevent further inflammation, slow cellular metabolism, provide a degree of discomfort relief, and prevent cellular uptake of the contrast media. Animal studies suggest that cold application has the greatest chance of reducing contrast media ulcerations compared with warm compresses.

Mixed evidence exists for the use of hyaluronidase for the management of contrast media extravasation injuries. In a histologic model, ani-
mals injected with hyperosmolar contrast media and concurrent hyaluronidase developed the most severe tissue damage; however, the contrast media studied was 1400 mOsm/kg or higher. A case series of 225 nonionic contrast media infiltrations described the clinical course of patients receiving hyaluronidase compared with conservative management. Hyaluronidase was more likely to be used in patients experiencing larger extravasation injuries (more than 50 ml). There were no serious complications in any of the patients who did not receive hyaluronidase during the 7-year observation period. Of the patients who received hyaluronidase, two patients with large infiltrations developed transient skin blistering that self-resolved after a week. These results may suggest many patients with limited infiltrations can be managed conservatively with close monitoring. There is only a single report describing the use of high-dose hyaluronidase for a large contrast media infiltra-
tion. The authors claimed successful resolution within 4 hours of injection of the enzyme, but this may have represented the patient's normal clinical course of infiltration. It may be reason-
able to consider hyaluronidase as a supplement to medical therapy for larger volumes of extravasa-
ted contrast media or if the patient appears at high risk for injury.

Acidic and Alkaline Agents

Infiltration of agents with a nonphysiologic pH may predispose patients to severe forms of tissue injury. Mechanisms of tissue injury in the context of extravasations remain unstudied. Extensive literature exists, however, on the mechanisms of tissue injury during caustic ingestions and topical exposures. Exposure of tissue to an alkaline solution leads to the result-
ant formation of dissociated hydroxide ions that penetrate tissues extensively. This leads to protein dissolution, collagen destruction, vasocon-
striction, fatty acid saponification, cell membrane compromise, and cellular apoptosis. Erythema and edema commonly follow, result-
ing from the inflammatory reaction induced by tissue damage. As the fascial layers are destroyed, the hydroxide ions continue to penetrate tissue until fully neutralized by proteins and tissue water. Acid exposure commonly leads to cellular desiccation, coagulative necrosis, and eschar formation. Edema, vaso-
striction, sloughing, and ulceration are common manifestations of acid-induced tissue injury; however, compared with alkaline exposures, acid-induced injuries are typically less penetrat-
ing due to coagulation. Of the two, alkaline exposure has the highest propensity for severe tissue damage due to the deeper tissue penetra-
tion. Predictors of tissue injury include duration of exposure, pH of the substance involved, and the “titratable reserve” of the product. Titratable reserve refers to the amount of neutralizing sub-
stance required to bring a buffered substance to a physiologic pH. Titratable reserve is directly
proportional to the extent of tissue damage because more tissue structures are compromised before the agent is neutralized. Of note, the arterial intima is particularly sensitive to changes in pH, which may account for the ascending thrombosis, severe necrosis, and gangrene reported with inadvertent intraarterial administration of acidic or alkaline drugs.67

Management of acidic and alkaline infiltrations remains supportive. Elevation, warm compresses, and attempts to remove the extravasated material are common nonpharmacologic treatment approaches. Neutralization should largely be avoided because this can produce exothermic or gas-forming reactions that may worsen tissue injury.66 Further study is needed on the development of safe neutralizing agents before they are used as a treatment modality.

Phenytoin

Dermal necrosis has been reported frequently with the use of phenytoin and may be associated with an increased hospital length of stay.68 The drug is commonly formulated with sodium hydroxide and propylene glycol, creating a resultant hyperosmolar product with a pH greater than 12.69 The product’s alkalinity may cause a direct vasoconstrictive response, followed by the breakdown of vascular integrity. The swelling may result from inflammation or the hyperosmolar contents of phenytoin and propylene glycol. Poor capillary circulation due to the edema may lead to development of increased compartmental pressures against the tissue structures in the hand. Some authors have proposed that the pH change that results from dilution of the product in the bloodstream may cause a precipitation of the product, resulting in thrombosis.11, 69 Tissue studies remain inconsistent in their detection of thrombi around the site of injury, although thrombosis has been detected in early phases of injury in animal studies.70 Animal studies have found that phenytoin causes a similar degree of necrosis even when formulated without propylene glycol, suggesting that the alkaline properties of the drug itself may be the chief culprit in tissue injury.69 With the exception of a few atypical cases, phenytoin-related soft tissue injury, or purple glove syndrome (PGS), is characterized by three phases of tissue damage. The first phase of the syndrome consists of pain and a purple-blue discoloration distal to the site of venous access. Over the next 6 hours, patients will develop a glove-like circumferential erythema accompanied by edema spreading from the cannula. A third of patients will progress to the third phase of injury that consists of bullae formation, absence of arterial flow, skin necrosis, or compartment syndrome.68 The incidence of PGS varies throughout the literature, from 1.7% to 5.9% of emergent phenytoin injections.68, 71 Risk factors for PGS include extremes of age, hemodynamic instability, number of administered doses, administration during the acute seizure period, and prior development of PGS.68, 72 The pathogenesis of PGS remains largely unclear. Although some patients develop the syndrome as a result of extravasation, many PGS cases develop without clinically apparent infiltration.68 Conversely, patients may have infiltrations without the development of any aspects of the syndrome. PGS has been successfully managed with conservative treatment measures such as elevation and dry heat. These early conservative treatment measures prevent the development of serious necrosis.68, 70 Intradermal hyaluronidase and topical nitroglycerin have also both been attempted, as described in single case reports, both with moderate degrees of success in combination with conservative therapies.73 Administration of the drug at a rate of lower than 20 mg/minute has been associated with a lower occurrence of PGS without interfering with time to seizure control compared with the product’s prodrug fosphenytoin.74 Dilution of phenytoin in normal saline (to achieve a concentration of 6.7 mg/ml) drastically reduces the occurrence of phlebitis that may lead to a reduction in the frequency of PGS.72 Use of fosphenytoin is reasonable in patients at particularly high risk for PGS because the product remains soluble without propylene glycol and is less alkaline.

Promethazine

Promethazine has emerged as a particularly caustic substance, with extravasations and arterial administrations leading to cases of tissue necrosis, gangrene, and amputation. Most of these case reports involve suspected inadvertent arterial administration of the drug, particularly common in areas around the skin and soft tissue structures of the hand and wrist.75 Extravasations causing severe tissue damage have also been reported. Variations in the anatomy of the radial and ulnar nerves may result in the subcutaneous presentation of these arteries along the hand and wrist, and predispose patients to inadvertent arterial administration.14 Patients presenting with
severe emesis may pose a particular risk for extravasation because it may be challenging to acquire peripheral access in the dehydrated state. Aspiration of dark blood does not particularly rule out an inadvertent intraarterial line; blood coming into contact with promethazine will become discolored or darkened. Unfortunately, there is no predictive of tissue necrosis or permanent sequelae induced by the insulting drug. Use of intraarterial, venous, or locally applied vasodilators such as papaverine, topical nitroglycerin, and iloprost have met with various degrees of success in the general treatment of foreign materials in the arterial circulation. A combination of systemic steroids, papaverine, and stellate ganglion blockade has also been attempted for the nonintraarterial extravasation of promethazine with a moderate degree of success.

Several methods have been proposed for the prevention of promethazine-induced tissue necrosis if the patient is refractory to alternative antiemetics. First, only the 25 mg/ml product should be supplied to dispensing areas, and it should be preferably diluted further with 10–20 ml of normal saline. Second, the initial dose should be reduced to 6.25–12.5 mg and escalated only if necessary. Third, the product should be infused through a larger bore vein (avoiding veins of the wrist and hand, if possible) over 10–15 minutes. Any early warnings of signs of pain, swelling, or cyanosis should warrant immediate cessation of the infusion and evaluation for intraarterial administration or extravasation.

Conclusion

Extravasation of diagnostic and therapeutic substances is a relatively frequent occurrence in patients receiving well-intended treatment. Extravasations can lead to substantial occurrences including pain, decreased mobility, and permanent nerve, soft tissue, and/or tendon damage. Severe extravasations may ultimately require aggressive tissue debridement, grafting, or extremity amputation. Preventive measures in high-risk situations, such as adequate monitoring and early recognition, remain the most optimal approach to extravasation injuries.

Upon extravasation of a high-risk substance, a multidisciplinary approach among nurses, pharmacists, the medical care team, and surgeons is often necessary to assess the chemical and pharmacologic properties of the infiltrated agent, the extent or potential for tissue damage, and the need for reversal or surgical intervention. The extravasated material must be assessed carefully for early signs of compartment syndrome and tissue damage. Therapy for extravasated materials must be administered in a timely manner before tissue damage becomes irreversible. An appropriate knowledge of the mechanisms of tissue injury caused by the chemical properties, recipients, or direct actions of the material infiltrated allows the clinician to select prompt and appropriate measures to attenuate further tissue injury.

Unfortunately, the evidence for the management of extravasation is largely limited to case reports and case series describing attempted treatment modalities. Reports on the treatment of particularly devastating substances are even more limited, possibly due to the liability associated with these cases. As such, predicting clinical manifestations, propensity toward severe sequelae, or response to treatment may be difficult. Further reporting is needed to describe the pathophysiology of tissue injury, clinical manifestations of extravasated materials, responses to chosen therapies, and risk factors for extravasation so that practitioners can effectively treat or prevent this iatrogenic injury.

References


47. Fitzcharles-Bowe C, Denkler K, Lalande D. Finger injection with high-dose (1:1000) epinephrine: does it cause finger necrosis and should it be treated? Hand (N Y) 2007;2:5–11.


Supporting Information

The following supporting information is available in the online version of this paper:

Appendix S1. Search Strategy.