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Recommendations for Management of Noncytotoxic Vesicant Extravasations

Jennie Ong, PharmD • Ruth Van Gerpen, MS, RN-BC, APRN-CNS, AOCNS®

ABSTRACT

To prepare clinicians to treat extravasation of noncytotoxic vesicants with antidotes and thermal compresses, a literature review was performed to identify noncytotoxic vesicants and to create evidence and consensus-based recommendations. The stage of injury and vesicant's mechanism of tissue injury dictate treatment. For a vasopressor extravasation, warm compresses and administration of a vasodilator are recommended. For osmolarity, pH, absorption refractory, and cytotoxic concentration-dependent vesicants, warm compresses and administration of hyaluronidase are recommended. Compared with potentially catastrophic costs of undertreatment, the cost of overtreatment is minimal.

Key words: compartment syndrome, emergency treatment, extravasation, hyaluronidase, infiltration, irritant, noncytotoxic vesicant antidote, phentolamine, soft tissue injury, terbutaline, tissue or skin necrosis, warm or cold compress

Extravasation is a universal risk of intravenous (IV) vesicant administration. Appropriate precautions can reduce the risk but not eliminate it. The terms *extravasation* and *infiltration* are often used interchangeably in the literature, but the 2016 *Infusion Therapy Standards of Practice* (the *Standards*)[1] defines extravasation as "inadvertent infiltration of vesicant solution or medication into the surrounding tissue,"[1(pS149)] whereas infiltration is the "inadvertent administration of a nonvesicant solution or medication into surrounding tissues."[1(pS150)] A vesicant is an agent capable of causing tissue damage when it escapes from the intended vascular pathway into surrounding tissue. Vesicant identification and consensus treatment recommendations existed as early as 1979[2] for cytotoxic vesicants, but it is only in recent years that extravasation injury from noncytotoxic vesicants has begun to receive similar attention. In 2017, the Infusion Nurses Society (INS) Vesicant Task Force published an evidence-based list identifying noncytotoxic vesicants,[3] but treatment modalities were outside the scope of that review. This article summarizes the evidence supporting treatments for noncytotoxic vesicant extravasations and contains recommendations to aid clinicians in making timely, evidence-based treatment decisions.

Authors' Affiliation: *Bryan Medical Center, Lincoln, Nebraska (Dr Ong and Ms Van Gerpen).*

Jennie Ong, PharmD, *is a clinical pharmacist at Bryan Medical Center in Lincoln, Nebraska, with 10 years of hospital pharmacy experience. Her specialties include formulary management and patient safety–oriented process improvements.* **Ruth Van Gerpen MS, RN-BC, APRN-CNS, AOCNS®,** *is a clinical nurse specialist at Bryan Medical Center in Lincoln, Nebraska, with 36 years of oncology experience. Her subspecialties include pain management and infusion therapy.*

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Corresponding Author: *Jennie Ong, PharmD, Bryan Medical Center, 1600 S. 48th St., Lincoln, NE 68506 (jennie.ong@bryanhealth.org).*

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BARRIERS TO APPROPRIATE AND TIMELY TREATMENT

A calcium extravasation was the impetus for seeking evidence-based treatment recommendations for noncytotoxic vesicant extravasations. Every source reviewed had different lists of noncytotoxic vesicants and varying recommendations and reasoning for proposed treatments. The lack of consensus in the literature contributes both to undertreatment and inappropriate treatment of extravasations. In the case of extravasation injury, the cost of overtreating is minimal. The antidotes are relatively inexpensive, easy to prepare, and cause minor if any discomfort to the patient. In contrast, the cost of undertreatment can be hospitalization, surgical intervention, and permanent cosmetic and functional defects. Identified barriers to receiving appropriate,

timely treatment include delayed recognition, unknown treatment options, lack of or inconsistent evidence supporting a treatment approach, and unknown or uncertain vesicant status of the medication.

Delayed Recognition

Despite recommendations in the *Standards*[1] to assess vascular access devices for signs and/or symptoms of infiltration and extravasation before each infusion and on a regular basis, some extravasations are recognized after irreversible damage has occurred, limiting the efficacy of intervention options. Loth and Eversmann[4] proposed the concept of a necrosis interval to guide therapy decisions. The necrosis interval is the time from extravasation until irreversible tissue damage occurs, and it varies for each vesicant. If the offending agent is counteracted or removed within the time interval, then necrosis is prevented. The necrosis interval has not been determined for every vesicant. However, because the interval can be quite short, for example 4 to 6 hours for vasopressors, extravasation should be considered a medical emergency requiring time-sensitive treatment. Recognition of extravasation outside the necrosis interval may preclude treatments that would prevent or reduce damage and instead necessitate damage control.

Unknown Treatment Options

To date there are no published articles that comprehensively describe the evidence supporting or refuting a wide variety of treatments for noncytotoxic extravasations. Even for treatment methods with documentation of efficacy, when confronted with drug shortages affecting first-line options such as phentolamine, second-line treatment options have not been as well documented.

Uncertainty as to Appropriateness of Treatment Options

Every extravasation is unique. No two will have identical factors influencing the extent of injury or treatment decisions. Both patient- and incident-specific factors influence treatment decisions. These factors can include age, weight, comorbidities, communication barriers, skin integrity, site of extravasation, anatomic anomalies, care setting, response to current treatment, timing of recognition, and, perhaps most importantly, the identity, amount, and concentration of the vesicant. With so many factors influencing treatment and prognosis, it may seem difficult or even impractical to apply evidence from one extravasation to another.

Despite the unique nature of each extravasation, all are identical in that the patient's tissues have inadvertently been exposed to a toxic substance. Tissue damage will occur unless the vesicant's toxicity and mechanism of tissue injury can be eliminated or reversed. Thus, extravasation treatments are generalizable when the mechanism of tissue injury and method to eliminate or reverse it are considered. Large, multicenter, randomized, double-blind, head-to-head, or placebo-controlled trials are the gold standard in evidence-based medicine. This level of evidence will never exist for extravasation, because ethical considerations preclude purposefully inflicting an extravasation on humans to test potential remedies. Perhaps, as a result of the varied nature of extravasations, the published recommendations and reported management of extravasations are just as varied. Conflicting recommendations and case reports describing a variety of treatment options have sometimes resulted in inappropriate therapy choices, such as applying cold compresses (instead of dry, warm compresses) to a norepinephrine extravasation. Applying reported or recommended treatments from one case to another should be done in the context of the mechanism of tissue injury and whether the proposed treatment is likely to eliminate or reverse the toxic potential of the vesicant.

Unknown or Uncertain Vesicant Status

Noncytotoxic vesicants are reported in many disparate lists. Even with all the evidence available, however, there are some medications that likely are vesicants but lack confirming evidence. These could include lower potency vesicants, those with a weaker propensity for causing tissue injury, or recently developed medications. Medications reviewed and ultimately excluded as noncytotoxic vesicants by the INS Vesicant Task Force[3] (mostly because of insufficient evidence), as well as infiltration of any medication not yet identified as a vesicant, may warrant extravasation treatment if symptoms of extravasation occur. A medication may be a vesicant although it is not yet recognized as one.

LITERATURE SEARCH AND METHODOLOGY FOR EXTRAVASATION MANAGEMENT IDENTIFICATION

The *Standards* recommends that "each facility should reach a consensus on what medication is considered to be a vesicant and irritant based on their internal formularies" and "identify the vesicant nature of antineoplastic and noncytotoxic medications prior to administration and be prepared to use the correct antidote treatment for each medication."[1(pS98)]

From published lists, 86 purported vesicants were identified. Inclusion in the vesicant list required either: (1) reports in literature or from manufacturer of tissue injury upon extravasation or (2) adverse effects or warnings in secondary drug information sources such as Micromedex or Lexicomp consistent with a vesicant along with a valid proposed mechanism of tissue injury.

Of the 86 purported vesicants vetted, 45 drugs met our inclusion criteria. This review, which began in August 2016, was bolstered in January 2017 when the INS Vesicant Task Force published an evidence-based list of noncytotoxic vesicants.[3] Of 42 purported vesicants vetted by Gorski et al,[3] 25 were classified as vesicants. The other 17 were

indeterminate at the time due to inconclusive or conflicting data. Based on more recent case reports, 3 of the 17 indeterminate vesicants (gentamicin, immune globulin, and propofol) met our first vesicant criteria. Of the remaining 14 indeterminate vesicants, another 8 met our first inclusion criteria (aminophylline, amphotericin, ampicillin, doxycycline, lorazepam, metronidazole, penicillin, and valproate). We had reviewed 44 purported vesicants that the INS Vesicant Task Force did not review, 4 of which met our first criteria (digoxin, lipids, methylene blue, and phosphate salts) and 5 of which met our second criteria (conivaptan, dantrolene, diazepam, esmolol, and etomidate). Radiographic contrast material is excluded from our recommendations due to the unique nature and scope of contrast extravasations. Other exclusions included antineoplastic vesicants, products not recommended for IV use, extravasations not involving skin or soft tissue (eg, intraperitoneal), and products not available in the United States.

Aside from the US Food and Drug Administration (FDA)-approved antidote phentolamine, literature support for antidotes and thermal compresses is largely limited to case reports or case series. More than 1800 cases were included in this review, but for treatments short on published evidence, published articles with recommendations have also been included to support a consensus recommendation. Previously published recommendations represent the authors' opinion, description of local practice, or institutional guidelines.

The US National Library of Medicine holdings in the PubMed database were searched without beginning date restriction through February 15, 2020, using the search string "Extravasation of Diagnostic and Therapeutic Materials" [Mesh] OR "Extravasation" [Title] OR (Infiltration OR extravasa*) AND drug AND "Humans" [Mesh]. Of the 23,159 titles or abstracts screened manually, the full text of 257 articles was sought. Because of the inability to translate or unavailability of the full text, 14 articles were excluded from full-text review. On bibliography screening, the full text of an additional 226 articles was reviewed. Of the 469 articles reviewed, 331 articles were ultimately included in the review, and 138 were excluded for the following reasons:

1. Chemotherapy extravasations (6 articles)
2. Vesicant not identified (25 articles)
3. Infiltration of irritant, not of a known vesicant (15 articles)
4. Adverse effect without extravasation, that is, a systemic effect (21 articles)
5. Norepinephrine untreated or phentolamine monotherapy, already FDA approved (15 articles)
6. Vesicant unavailable in the United States (mezlocillin/sulbactam, metiamide, toluidine blue) (3 articles)
7. Noncontributory in either recommendations or cases (45 articles)
8. Anatomically distinct extravasation (eg, intra-arterial or neonatal umbilical vein) (8 articles). For a thorough list of other articles describing anatomically distinct extravasations, see Appendix 2 of Corbett et al.[5]

In conversation with J. Friedman, MD (July 11, 2019), and written communication with J. L. Thigpen, RNC, MN (November 1, 2019), V. Boyar, MD (November 2, 2019), and J. C. Schie, MS, OTR/L (November 18, 2019), we were able to clarify which drug extravasated in several previously published cases.[6-9] Medication prescribing information was also used. Pertinent landmark animal case studies were also reviewed.

MECHANISMS OF TISSUE INJURY

Vesicant classification by mechanism of tissue injury is useful in determining appropriate management to eliminate or reverse the toxic potential of an extravasate. The 4 widely recognized mechanisms of tissue injury are pH, osmolarity, vasoconstriction, and cytotoxicity. We propose absorption refractory as a new fifth mechanism of tissue injury.

Nonphysiologic pH

Physiologic pH is 7.35–7.45. Extreme pH exposure, typically defined as a pH of <5 or >9,[10] can damage venous endothelium and increase risk of vessel rupture. When agents with extreme pH extravasate, they can cause damage in the same manner.[11,12] Tissue destruction and vasoconstriction with resulting inflammatory response, edema, sloughing, and 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.[13]

Osmolarity

Physiologic osmolarity is approximately 310 mOsm/L.[14] Both 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. The generally accepted cutoff for hypotonicity and risk of hemolysis with IV infusion is <112 mOsm/L,[15] whereas for hypertonicity and risk of being a vesicant the cutoff is >900 mOsm/L.[16] Hypertonicity disrupts cellular ion transport and causes fluid shift from cells to the interstitial space, which may lead to swelling and compartment syndrome. Histopathology confirms, for example, that extravasation of 10% calcium chloride, which has an osmolarity of 2050 mOsm/L, is "a true 'subcutaneous burn' and as such involves both the overlying skin and the underlying fascia and skeletal muscle."[17(p155)] High osmolarity vesicants, including phosphate and calcium, also present a precipitation risk. Calcium precipitation in soft tissues is called *calcinosis cutis* and can occur with or without accompanying necrosis.[1,18-20]

Vasoconstriction

Localized vasoconstriction attributed to extravasation can result in ischemia and necrosis by reducing blood flow.

Vesicant exposed tissues are at risk from both chemically induced and mechanically induced vasoconstriction. Electrolyte solutions such as calcium and sodium, along with pharmacologic vasopressors such as dopamine and epinephrine, can chemically induce vasoconstriction. Large volume or anatomically trapped extravasations can mechanically induce vasoconstriction when the interstitial pressure is raised enough to overcome the venous pressure, blocking blood flow and even causing compartment syndrome.

Cytotoxicity

Cytotoxicity is primarily associated with antineoplastic drugs. For antineoplastic drugs, extravasation injury occurs as a result of the vesicant binding to the nucleic acids in the DNA of healthy cells in the tissue causing cell death. Other cytotoxic vesicants damage cells or tissues on coming into direct contact with them. The identity and treatment of antineoplastic vesicants have been published elsewhere and are outside the scope of this review.[21]

Absorption Refractory

Absorption refractory is a newly proposed mechanism of tissue injury whereby drugs with insolubilities or limited ability to be absorbed into the bloodstream persist in the extravasated space. The prolonged presence of lipids in the interstitial space has led to deep tissue necrosis, and propofol, often contained in a lipid carrier solution, seems particularly prone to causing necrosis and compartment syndrome because of its limited ability to disperse in the tissues and be absorbed into the bloodstream.[22-36]

MANAGEMENT RECOMMENDATIONS

Effective extravasation management requires early recognition of signs and symptoms and prompt implementation of appropriate clinical management strategies.[1] Extravasation is unique, but the patterns of initial symptoms are commonly staged as first proposed by Millam in 1988[37] and validated in a pediatric population by Flemmer and Chan in 1993.[38] Published iterations of this staging are used widely for patients of all ages. Strengths from multiple versions have been refined, and the resulting proposed staging recommendations can be found in Table 1.[4-6,37-40] Extravasations of small volume with less potent vesicants are likely to fit into stages 1 or 2, whereas more potent vesicants and/or larger extravasated volumes will tend to reach stages 3 or 4. Once the necrosis interval has passed (which can be as short as 4 to 6 hours for vasopressors), the staging table is no longer relevant, and assessments should be made based on whether the injury is receding or advancing.

TABLE 1

Extravasation Staging

Stage	Assessment	Treatment options
1	• Painful infusion site • No erythema • Localized swelling (1%-10% of extremity above or below site)	• Remove cannula • Elevate extremity • Warm/cold compresses
2	• Painful infusion site • Slight swelling at site (up to 25% of extremity above or below site) • Slight erythema (localized to the central area of extravasation) • Good pulse below site • Brisk (1-2 s) capillary refill below site	• Remove cannula • Elevate extremity • Warm/cold compresses • Consider antidote
3	• Painful infusion site • Moderate swelling at site (25%-50% of extremity above or below site) • Marked erythema (extends beyond central area of extravasation) • Blanching (for vasopressor extravasation only) • Good pulse below site • Brisk (1-2 s) capillary refill below site • Skin cool to touch	• Leave cannula in place; using a 1 mL syringe, aspirate as much fluid as possible • Remove cannula unless it is needed for antidote administration • Elevate extremity • Warm/cold compresses • Consider antidote
4	• Painful infusion site • Severe swelling at site (>50% of extremity above or below site) • Very marked erythema (extends beyond borders of swelling) • Blanching (nonvasopressor extravasation) • Decreased or absent pulse • Prolonged capillary refill >4 s • Skin cool to touch • Skin breakdown including blistering or necrosis	• Leave cannula in place; using a 1-mL syringe, aspirate as much fluid as possible • Remove cannula unless it is needed for antidote administration • Elevate extremity • Warm/cold compresses • Consider antidote • If swelling of the site is tense and skin is blanched, obtain surgical consult

Data from Loth and Eversmann,[4] Corbett et al,[5] Friedman,[6] Millam,[37] Flemmer and Chan,[38] Baharestani,[39] and Odom et al.[40]

Where treatment options have limited evidence supporting efficacy, clinicians must consider the potential benefits of the treatment and initiate those therapies where the benefits outweigh the risks. More invasive extravasation treatments are associated with greater risks, but they are also associated with faster onset and greater impact. Recommended initial treatment options ranked in order from least to greatest impact and risk are as follows: elevation, thermal therapy, antidote administration, saline flush out, and open incision with irrigation. Extravasation management for stage 1 and 2 injuries should begin with elevation and thermal therapy and advance to antidote administration at 30 minutes if the injury is not resolving. Because stage 3 and 4 injuries are unlikely to downstage with the impact of elevation and thermal compresses alone, antidote therapy should be initiated immediately.[38] If the injury has not downstaged or is not resolving by 30 to 60 minutes after the initial antidote, consider repeating antidote administration or switching to alternative antidote until symptoms begin to resolve. If at any point it appears that antidote administration will not be sufficient to prevent extensive injury, consider immediately advancing to a saline flush out or open incision and irrigation.[41,42] The level of treatment should be proportional to the level of injury and should err on the side of overtreatment when it comes to antidote administration, because the costs of antidote overtreatment are minimal when compared with the potential costs of undertreatment. The impact of elevation and thermal compress therapy on symptom resolution is small when compared with the impact of antidote administration or saline flush out.

For pH-mediated, osmolarity-mediated, and absorption refractory extravasations, the goal is to dilute the vesicant through absorption and dispersal, so the appropriate antidote is hyaluronidase. Cytotoxic vesicants with concentration-dependent toxicity can also be treated with hyaluronidase. Vasodilators, such as phentolamine, terbutaline, or nitroglycerin, should be used to counteract vasoconstriction, whether caused by a vasoconstrictor, chemical vasoconstriction, or mechanical vasoconstriction. Table 2[43-297] contains antidote recommendations for each noncytotoxic vesicant. Additional antidote and treatment evidence not definitively linked to a particular vesicant is presented in Table 3. [298-304]

The clinical practice setting will influence which treatments are available. Initiate as much treatment as is indicated and possible. If the injury has not downstaged to level 1 with the maximum level of care the current setting can accommodate, clinicians should consider transferring the patient to a hospital with plastic surgery capabilities while there is still potential to prevent the damage rather than transferring the patient for debridement and skin grafting after the damage has occurred.

Overview of Treatments

The toxicity of vasoconstrictive vesicants can be reversed by vasodilator administration, but pH, osmolarity, and even to some extent cytotoxic vesicants have concentration-dependent toxicity. To dilute the vesicant to eliminate its toxicity, it must either be absorbed into the bloodstream or dispersed among interstitial fluids. Hyaluronidase facilitates both. An FDA-approved indication of hyaluronidase is as an adjuvant to increase the absorption and dispersion of other injected drugs.[305] This can be used, for example, as a planned enhancement to localized analgesia, but with extravasation it is used as an unplanned rescue attempt to facilitate dispersion and absorption into the bloodstream from the extravascular space. The use of hyaluronidase for extravasation injury is not FDA approved and is therefore considered "off-label."

Hyaluronidase facilitates absorption and dispersal of drugs and fluids by dissolving hyaluronic acid, one of the binders that holds soft tissue cell layers together and forms the dermal barrier. By loosening the layers from each other, fluid is able to flow freely between sheets of tissue. "The rate and extent of dispersion and absorption is proportionate to the amount of hyaluronidase and the volume of solution."[305p6] A 150-unit dose of hyaluronidase will facilitate the absorption of 1 L or more of subcutaneously administered fluid.[305] In studying hyaluronidase for hypodermoclysis, Hallman et al[306] used each pediatric patient as their own control, receiving subcutaneous fluids in both legs but hyaluronidase in only one leg. Without regard to bolus volume (range, 20–40 mL) or fluid type (saline or dextrose), hyaluronidase accelerated absorption in every measurable case (anatomy precluded measurement in 2 patients). On average, hyaluronidase accelerated absorption time to 84 minutes versus 214 minutes without hyaluronidase. In 2 cases in particular, skin tension decreased within only 2 minutes of hyaluronidase administration.[306] The dermal barrier does not reform in full until approximately 48 hours later in a dose-dependent manner.[305]

Hyaluronidase is an effective mainstay of extravasation treatment. In 1950, Haire[307] reported that the pain, swelling, and induration caused by extravasation of neoarsphenamine in one case and mapharsen in another resolved completely within 24 hours after treatment with 250 units of hyaluronidase. He reported that the amounts extravasated in these cases would normally have caused a painful induration lasting for weeks. Acceptance of hyaluronidase to treat extravasation injuries grew and was mentioned in surgical textbooks as early as 1953.[308] Although ethical considerations preclude the study of hyaluronidase versus placebo for extravasation injury in humans, Zimmet[309] demonstrated in rats that, after injection with 23.4% sodium chloride, hyaluronidase-treated rats had a decreased incidence of ulceration (50%) versus normal saline or water (80%). The average ulceration size in the normal saline and water groups was 2 to 3 times as large as in the hyaluronidase groups. Similarly, Laurie et al[310] demonstrated in rabbits that after parenteral nutrition injection, rabbits receiving no treatment had ulcers on average 13 times as large as hyaluronidase-treated rabbits. After injection with calcium

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]
Calcium gluconate or calcium gluceptate Calcinosis cutis without necrosis	Monitor superficial calcifications closely as many resolve spontaneously.[13] Alternative: sodium thiosulfate[13,58]	Sodium thiosulfate: 1 case where treatment started day 83 after inadequate response to warm compresses; improvement began day 100 with eventual full resolution.[102]	Conservative: 33 cases healed without sequelae.[87-89,103-116] Five cases healed with permanent cosmetic deficit[108] and 1 case had PFD.[105]
Dextrose ≥10% 10% solution: 505 mOsm/L[3]	Hyaluronidase[13,44-49,54-56,58]	Hyaluronidase: 1 case necrosed, but 7 had no injury including 1 case treated with incisions for fluid outlet and 1 co-extravasation with calcium[7,44,45,51,60,61,117-119]	Flush out: 1 case necrosed[99] Flush out and aspiration: 1 case necrosed[120] Conservative: 30 of 40 cases necrosed, including 14 that required surgery with 8 cases of PFD. One nonsurgical case had PFD.[42,63-65,67,68,70,79,80,85,99,121-126]
Diazepam: >2000 mOsm/kg[10]	Hyaluronidase[13]		Conservative: 2 necrosed and had PFD.[64]
Digoxin Cytotoxicity and vasoconstriction are additional mechanisms of tissue injury[127]	Hyaluronidase[13]		
Etomidate: 4965 mOsm/L[128]	Hyaluronidase[13]		
Lorazepam: >2000 mOsm/kg[10]	Hyaluronidase[13]		
Mannitol ≥20% 20%: 1100 mOsm/L[43]	Hyaluronidase[13,47-48,56,58]	Hyaluronidase: 2 cases had no necrosis, including 1 case treated with cold packs.[23,129]	Compartment syndrome: 4 cases[130-133] Conservative: 1 bullae case required surgery.[134]

(*continues*)

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
Nafcillin 40 mg/mL:402 mOsm/kg[43]	Hyaluronidase[13,44-46,48,49,55]	Hyaluronidase: 2 cases of injury prevention.[135]	Conservative: 5 cases necrosed including 1 that required surgery.[136,137]
Parenteral nutrition: >900 mOsm/L	Hyaluronidase[13,44-49,55,56,58]	Hyaluronidase: 8 of 29 cases necrosed of which 2 had surgery.[6,9,60,117,138,139,139a] Hyaluronidase, flush out, and aspiration: 4 of 27 cases necrosed.[44,45,85,139a,140-142] Chondroitinsulfatase (like hyaluronidase, used in France): 2 cases had no necrosis.[143]	Incisions for fluid effluent: 9 of 12 cases necrosed and required surgery.[144] Another unspecified number had no necrosis.[145] Open incision and irrigation: 4 of 26 cases necrosed.[42] Surgical drainage: 1 case had no necrosis[146] Flush out and aspiration: 8 of 27 cases necrosed, 4 of which required surgery.[99,147] Compartment syndrome: 2 cases.[42,148] Nitroglycerin patch: 1 case without injury where the patch had been, but a necrotic lesion formed next to the patch site.[149] Conservative: 314 cases of which 273 had necrosis. The severest were 38 cases that required surgery with 7 cases of PFD. One death occurred.[6,8,40,42,63-65,68,70,76,92,99,121,122,139a,149-165]
Potassium chloride 20 mEq/100 mL: 400 mOsm/L 40 mEq/100 mL: 799 mOsm/L[3]	Hyaluronidase[13,44-49,55,56]	Hyaluronidase: at least 1 case of injury prevention[44,45]	Conservative: 17 of 18 cases necrosed (1 each a co-extravasation with calcium gluconate, 5% dextrose, diazepam, hypertonic saline and 2 cases with 5% dextrose in 0.45% saline). One case had compartment syndrome (a co-extravasation with 5% dextrose). Six of 11 severest surgery cases had PFD. One nonsurgical case had PFD.[40,64,80,92,121,166-170] Lidocaine nerve block in 1 case failed to prevent necrosis and required surgery[171]
Sodium bicarbonate ≥8.4% 4.2%: 1000 mOsm/L 8.4%: 2000 mOsm/L[43]	Hyaluronidase[13,45-47,49,56] Hyaluronidase or lidocaine recommended by manufacturer[172]	Hyaluronidase and flush out: 1 of 2 cases necrosed.[41,173]	Conservative: 23 of 25 cases necrosed, including 16 surgery cases of which 2 had PFD. Two nonsurgical cases had PFD.[23,41,70,80,85,123,174-177] Incision and drains: 1 case necrosed.[167]
Sodium chloride ≥3% 0.9% 308 mOsm/L[43] 3% 839 mOsm/L[3]	Hyaluronidase[13,45,48-50]		Conservative: 3 of 18 cases had injury (1 was a co-extravasation with propofol), 2 had no injury, and 13 cases didn't specify injury. [85,178-180]
Sodium phosphate: 7000 mOsm/L[43]	Hyaluronidase[13]		Conservative: 3 cases of persistent plaques, 1 of which had ulceration.[181]
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]

(*continues*)

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
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]
Immune globulin: pH 4-7.2[43]	Hyaluronidase for osmolarity and acid/base vesicants[13]	Hyaluronidase: 1 case with no necrosis.[60] Hyaluronidase before or with subcutaneous infusion: 2 cases necrosed with small scarring.[197]	Conservative: 3 of 5 cases necrosed.[23,85,99,198]
Pentamidine: pH 4.5-7.5[43]	Hyaluronidase[13]		Conservative: 1 case necrosed with PFD.[199]
Pentobarbital: pH 9-10.5[43]	Hyaluronidase for acid/base vesicants[13]		
Phenobarbital: pH 9.2-10.2[43]	Hyaluronidase[13,49]		Conservative: 1 case had bullae and 1 had necrosis and surgery.[200,201]
Phenytoin: pH 10-12.3[43] Precipitation an additional mechanism of injury[127]	Hyaluronidase[13,46-49,118] Alternative: nitroglycerin discussed, but not explicitly recommended.[13,46]	Hyaluronidase: 1 case had no necrosis[202] Hyaluronidase, flush out, and cold pack: 1 case had no necrosis.[203] Nitroglycerin (patch) and dry heat: 1 case of fasciotomy prevention.[204]	Flush out with lactated Ringers: 1 case had no necrosis.[205] Conservative: 56 of 63 cases necrosed, including 18 that required surgery with 10 cases of PFD and 1 nonsurgical PFD; 4 cases were treated with local heparin, heparinoid, or steroid therapy.[5,80,99,206-220]
Promethazine: pH 4.0-5.5[43] Cytotoxicity an additional mechanism of injury.[127]	Hyaluronidase[13]		Papaverine (oral), stellate ganglion block, systemic steroids: 1 case necrosed with persistent cold intolerance.[221]
Vancomycin: pH 2.5-4.5[43]	Hyaluronidase[13,46-49,55,56]		Conservative: 4 cases, of which 2 had bullous lesions and 2 had necrosis, including a co-extravasation with parenteral nutrition and Zosyn that required surgery.[222-225]
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]

(*continues*)

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
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]
Unknown mechanism of tissue injury			
Amphotericin: pH 5-7[43] 100 mg/L in dextrose 5%: 265 mOsm/kg[10]	Authors recommend: hyaluronidase and for liposomal amphotericin consider flush out.		Aspirin; ice for 24 h then heat: 1 case without injury.[227] Oxygen therapy, heat, and 20% dextrose dressings: 1 stage IV case with co-extravasation of dopamine, amphotericin, famotidine, fentanyl, amikacin, and meropenem. Complete recovery by day 12.[228]
Metronidazole: pH 5.5 (range 4.5-7.0) 310 mOsm/L[43]	Authors recommend: Hyaluronidase		Conservative: 1 case without injury.[229] Aspirin, pentoxifylline, and nifedipine: 1 case of necrosis required surgery.[230]
Penicillin: pH 5-8.5[43] Iso-osmotic[43]	Hyaluronidase [46,49,50,55,56,118]		Conservative: 2 co-extravasations with gentamicin necrosed.[23,72]
Valproate: pH 7.6[43] Variable osmolality[43] Toxicity to skin structures is a proposed mechanism of injury[232]	Authors recommend: consider hyaluronidase with flush out.		Conservative: 1 case required surgery.[232]
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]

(*continues*)

TABLE 2

Antidote Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Antidote recommendations	Antidote cases	Other treatments
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]
Methylene blue: pH 3-4.5[43] Cytotoxicity[127] and pH[43] are additional mechanisms of injury.	First line: nitroglycerin[13,58] Second line: phentolamine or terbutaline (for adrenergic antagonist)[13,58]		Conservative: 3 cases necrosed, including 2 surgery cases with 1 PFD.[275-277] Lymph mapping (1 bone marking): • Conservative: 21 of 47 cases necrosed, including 9 that required surgery.[278-284]
Norepinephrine	First line: phentolamine FDA approved[285] Second line: terbutaline[13,231,233] or nitroglycerin[13,46,58]	Phentolamine and nitroglycerin: 16 cases without injury.[243] Phentolamine and hyaluronidase: 15 cases without injury.[286] Axillary block and surgical vein decompression mitigated damage after inadequate phentolamine response.[287]	Stellate ganglion block at 48 h and vein decompression at 72 h mitigated the damage.[287] Flush out: fully recovered at 4 wk.[167] Conservative: 4 cases at stage 1 or 2 without injury.[288]
Phenylephrine	First line: phentolamine[13,45-47,49,50,56,58,231,236] Second line: nitroglycerin[13,46,58]		Conservative: 2 of 16 cases necrosed and required surgery.[288-291]
Vasopressin	First line: nitroglycerin[13,48] Second line: phentolamine [13,50] or terbutaline[13]		Stellate ganglion block and heat: 1 norepinephrine co-extravasation without injury[292] Conservative: 5 cases necrosed and required surgery, with 1 case of PFD.[293-297]

Abbreviations: FDA: US Food and Drug Administration, PFD: permanent functional deficit.

chloride, ulcer size in normal saline-treated and untreated rabbits was on average more than twice as large as hyaluronidase-treated rabbits. When hyaluronidase treatments in calcium chloride injected rabbits were delayed by 1 hour, the benefits remained statistically significant, but at 30 minutes, 3 hours, 6 hours, and 12 hours, hyaluronidase trended toward benefit but did not reach significance ($P = .1$, $P = .3$, $P = .5$, and $P = .2$, respectively). The authors theorized that the acute inflammatory phase at 30 minutes postextravasation inhibited the benefit of hyaluronidase and that the positive impact then began to wear off after the 1-hour mark. Timely administration of hyaluronidase can promote complete absorption of a vesicant before the necrosis interval is reached, thus preventing permanent damage.

The effect of hyaluronidase in the treatment of accidental extravasation is rapid and marked. The effect of hyaluronidase has been described as "immediate blanching of the overlying erythematous skin and dramatic decrease in swelling,"[202(p246)] that "within 5 minutes of hyaluronidase administration, the infant's foot developed a pinker hue and began to soften."[51(p187)] "Within 30 minutes, the patient's pain lessened, erythema abated, and soft tissue swelling was noted to improve."[119(pp257,e1)] More objectively, in 1 patient after only 15 minutes, the dorsalis pedis pulse that had been nonpalpable was again palpable,[51] and in a second case after a repeat administration of hyaluronidase, the radial and superficial palmar pulses, which had been absent to auscultation, were once again present.[202] Others have described the effect as "swelling and redness markedly decreased" over the 5-hour observation period and the patient's limb was normal sized again at 24 hours.[118(pp886,e4)] In the author's experience, a patient's intense itching and burning sensation from amiodarone extravasation completely resolved within 90 minutes of hyaluronidase administration without any adverse effects. Hyaluronidase is a highly effective, inexpensive therapy that can be administered with minimal discomfort.

Pharmacologic Antidotes

Hyaluronidase

For adult and pediatric patients, 15 units (up to 150 units) is typically administered subcutaneously in 5 divided doses of 0.2 mL each on the periphery of swelling like the points of a star. Repeat dosing every 30 to 60 minutes until desired effect is achieved. Total doses up to 450 units have been used without adverse effect.[45,59]

Sodium Thiosulfate

Calcinosis cutis treatment for adults is 12.5 g IV over 30 minutes and may increase gradually to 25 g 3 times per week.[13,102] Sodium thiosulfate combines with calcium to create calcium thiosulfate, which has a solubility between 250 and 100,000 times greater than other calcium salts.[311]

For acute extravasation treatment and calcinosis cutis prevention, mice treated with 0.1 mL of 25% sodium thiosulfate intradermally after injection with 0.12 mL of calcium gluconate had reduced incidence of calcification versus untreated mice (13% versus 53%) and 100% resolution of all ulcerations by day 21 versus only 73% resolution in untreated mice.[311]

Phentolamine (α1 Antagonist)

For adult and pediatric patients 5 to 10 mg in 10 to 20 mL of normal saline is typically administered intradermally in 5 divided doses on the periphery of blanching like the points of a star. This may be repeated every 30 to 60 minutes until desired effect or patient experiences an intolerably low blood pressure. Half-life in the bloodstream is 19 minutes.[285] Doses as low as 0.5 mg have been used initially in adults, and Zenk et al[45] recommend 0.5 mg as the starting dose in neonates.[257]

Terbutaline (β2 Agonist)

For adult and pediatric patients, terbutaline 1 mg in 10 mL of normal saline is typically administered intradermally in 5 divided doses on the periphery of blanching like the points of a star.[233] This may be repeated every 30 to 60 minutes until desired effect or patient experiences intolerable systemic effects, such as tachycardia or irregular blood pressure. The drug's half-life is 2.9 hours.[312]

Topical Nitroglycerin (Peripheral Vasodilator)

Apply 1 inch topically for adults and 4 mm/kg for neonates to affected area every 8 hours as needed until symptoms resolve.[242,245]

Nonpharmacologic and Supportive Therapies

Other than thermal therapy with warm or cold compresses, the use of supportive therapies is outside the scope of this review. They are presented merely to illustrate which therapies could be considered without a recommendation for or against their use.

Elevation

Yucha et al[313] tested intentional 5-mL infiltrations of 0.45% saline and 3% saline when the infiltrated arm was kept at the level of the heart versus elevated by 4 inches. They found no difference in pain scores, induration size, or infiltrate volume. This could have been attributed to the low volume of infiltrate or the small difference in elevation angle. Elevation may have a greater impact with a larger volume of infiltrate, for example 50 mL, or with a steeper angle of elevation, which has been used in neonates.[300]

Warm and Cold Compresses

Compresses can be applied at 15-minute intervals 4 times daily, although continuous use of up to 72 minutes on initial extravasation has been reported.[314] Cold compresses should be used when the goal is to localize and limit the spread of the vesicant to mitigate the damage, such as with cytotoxic vesicants.[50] Cold compresses should be used to treat extravasations of valproate, because the proposed

TABLE 3

Case Series Not Linked to a Specific Vesicant

Extravasates (# of cases)	Total number of cases	Treatments	Outcomes
Calcium, dextrose (high concentration), inotropes, parenteral nutrition, potassium, sodium bicarbonate[298]	56	Surgical saline flush out	No skin or soft tissue damage reported and no patient required reconstructive surgery.
Blood (1), calcium (20), chemotherapy (39), contrast (1), dextrose 10%-20% (6), dobutamine (1), flucloxacillin (2), heroin (2), parenteral nutrition (14), potassium (3), sodium bicarbonate (4), thiopentone (3)[41]	96	37 patients treated with surgical saline flush out, 1 with liposuction and 6 with both	39 patients with no skin damage and 5 patients with only minor skin blistering or delayed healing, compared with 52 patients initially treated conservatively of which 26 required surgical intervention.
Calcium gluconate (4), doxorubicin (4), parenteral nutrition (7)[299]	15	10 treated with surgical saline flush out (with hyaluronidase in 2 cases). Five managed conservatively.	7 flush out patients with no symptoms. 2 flush out patients healed without need for skin graft. 1 flush out patient and 5 conservative management (late referral) patients treated with artificial skin with no functional deficits and acceptable cosmetic defects.
Albumin (1), antibiotics with dextrose 5% in 0.22% sodium chloride (7 cases), blood (2), chemotherapy (5), dextrose 5% with potassium chloride (30 mEq/L) in 0.45% sodium chloride (1), dopamine (1), heparin (2), intralipid (1), and parenteral nutrition: no additives (13), with antibiotics (6), with contrast (1). Antibiotics included nafcillin, chloramphenicol, oxacillin, ampicillin, carbenicillin, cephalothin and gentamicin.[300]	34	Conservative management and wound care (silver sulfadiazine, povidone iodine, saline dressings)	No notable difference between treatment groups. No skin grafts required.
Calcium chloride (2), cloxacillin (1), epinephrine (2), dextrose 10% (5), parenteral nutrition without lipids (8), phenytoin (1), potassium chloride (11), sodium bicarbonate (1), vancomycin (1). Some patients had more than one drug extravasate.[47]	34	Hyaluronidase in 14 patients (including inappropriately in 1 epinephrine case)	No adverse effects of hyaluronidase. Outcomes not reported. Authors' note: reported that 34 extravasations should have been treated with an antidote according to published protocol, but upon reviewing list of extravasates and protocol, only 32 cases appear to have been eligible for antidote administration.
Aminophylline and insulin (1), blood (5), calcium and 10% dextrose (5), dextrose 10% and magnesium (1), flucloxacillin and dextrose 10% (1), parenteral nutrition (14), platelets (1), sodium bicarbonate (2), tromethamine (2). (4 cases had co-extravasation of 2 solutions).[301]	28	Hyaluronidase and saline irrigation (10). Saline irrigation without hyaluronidase (2).	Survey inclusion required that necrosis had developed.
Contrast (4), ciprofloxacin (3) dextrose 10% (4), dopamine (5), fentanyl (3), parenteral nutrition (38), potassium chloride (4). Other agents less than 3 cases each (29).[302]	90		Parenteral nutrition: 31 cases treated with hyaluronidase. 46 of 90 cases fully recovered, 10 required wound care referral, 44 outcomes not documented.
Not reported[303]	115	Hyaluronidase in 110 peripheral cases (3.9% of peripheral lines placed) and 5 midline cases (1.2% of midlines placed).	Outcomes not reported; 24 significant midline catheter infiltrations not treated with hyaluronidase. Original author unable to provide additional information.

(*continues*)

TABLE 3

Case Series Not Linked to a Specific Vesicant (*Continued*)

Extravasates (# of cases)	Total number of cases	Treatments	Outcomes
Cyclophosphamide (1), dextrose 5% in 0.45% sodium chloride with 20 mEq potassium chloride/liter (2), lipids and parenteral nutrition (2), unreported (142).[40]	147	Heat (32), elevation (9), heat and elevation (28), cold (3), hyaluronidase (25). phentolamine (1), no treatment (49).	Only grade 3 or 4 injuries included. No surgical intervention required, no compartment syndrome. Severe stage 4 injuries from reported extravasates treated by wound care team with healing over 17 d on average. Original author unable to provide additional information.
Not reported.[304]	4	Active leptospermum honey and dehydrated amniotic membrane allograft.	Healing in 27, 34, 21, and 41 d, respectively.
Included amino acids and calcium.[157]	61	Initial treatment not reported.	30 barely perceptible scars from fluid infiltration or extravasation. 31 noticeable scars including 4 significant cosmetic or functional scars. 1 of the 4 significant scars was due to parenteral nutrition. Also 3 patients with areas of alopecia from infiltration. 100 NICU graduates assessed for scars.
Antibiotics[85]	13	Conservative treatment	Healed without necrosis
Drugs[117]	10	Hyaluronidase for stage 3 or 4 injuries	3 cases were stage IV and received hyaluronidase. No patients required debridement or skin grafting.
Calcium chloride and/or dextrose 10%[126]	15	Conservative management	Only stage 3 or 4 injuries included. Scarring in every patient. 4 patients required surgery.

Abbreviation NICU, neonatal intensive care unit.

mechanism of tissue injury is toxicity to skin structures.[232] Warm compresses in conjunction with vasodilatory antidotes (phentolamine, terbutaline, and nitroglycerin) should be used for extravasation of vasoconstrictive vesicants where the goal is to increase circulation. For pH-mediated, osmolarity-mediated, absorption refractory, and even some cytotoxic concentration-dependent vesicants, the goal is to disperse and absorb the vesicant, so warm compresses should be used along with the antidote hyaluronidase.[13,50] Vesicants containing fats, including 3-in-1 parenteral nutrition and the absorption refractory vesicants propofol and lipids, will experience improved absorption and distribution with warm compresses because of improved solubility and decreased viscosity of fats with increased temperature. "Use of dry heat in conjunction with hyaluronidase works synergistically to increase blood flow and disperse the extravasated drug."[1(pS100)] Hastings-Tolsma et al[314] demonstrated that warm compresses are effective at aiding in dispersion of infiltrated fluids, whereas cold compresses tended to keep the fluids trapped. Eighteen patients had 5 mL purposefully infiltrated; 6 with 0.45% saline, 6 with 0.9% saline, and 6 with 3% saline. At 12, 42, and 72 minutes postinfiltration, the 9 patients with warm compresses had statistically significantly lower infiltrate volumes remaining ($P < .001$) versus the 9 patients with cold compresses (3 in each concentration group). Thermal compress therapy is not without risks and should be performed carefully.[236,315] See Table 4 for thermal compress recommendations.[316-332]

Physical Massage or Compression Therapy

To manually aid in fluid dispersion and reduce tissue pressure, physical massage can be used, or an inflatable splint can be placed on a neonate and inflated for a portion of every hour to physically disperse infiltrated fluid that is anatomically trapped.[333,334]

Localized Steroid Therapy

Topical or locally injected steroids have been reported with mixed results. Ahn et al[335] found in rabbits that triamcinolone therapy seemed to reduce the reaction but was unable to prevent calcinosis cutis. Compaña et al[311] conversely found that, in mice, triamcinolone therapy actually worsened the extent of the reaction.

Antimicrobial Therapy

Topical and systemic preventive antimicrobial therapy have been reported. Silver sulfadiazine cream can be used, because extravasation is a chemical burn. Secondary

TABLE 4

Thermal Compress Recommendations for Noncytotoxic Vesicants

Vesicant	Thermal compress recommendations: Primary	Thermal compress recommendations: Secondary	Supportive literature
Osmolarity mediated tissue injury			
Aminophylline	Warm[13,50]	Warm or cold[13,58] Cold[46]	None available
Ampicillin	Warm[50]	Warm or cold[13] Cold[56]	Co-extravasation with cefotaxime, dextrose 10% in 0.225% sodium chloride. Warm packs inadequate, so hyaluronidase used resulting in no necrosis.[51]
Calcium chloride	Warm[50,58]	Warm or cold[13] Cold[56]	Calcinosis cutis and fat necrosis resolved over 4 weeks with warm wet compresses.[316]
Calcium disodium edetate (EDTA)	Warm[317]		Calcinosis cutis that required surgical excision despite use of warm soaks.[317]
Calcium gluconate	Warm[50,58]	Warm or cold[13]	1 case of inadequate response to dry heat that required sodium thiosulfate.[102] 3 cases of necrosis despite use of warm soaks.[87,88,318] 11 cases of necrosis despite use of cold compresses (with saline flush out in 9 cases).[86,319,320]
Dextrose	Warm[50]	Warm or cold[13] Cold[46,56,58]	3 cases used cold compresses of which 2 cases with hyaluronidase had no necrosis, whereas the case without hyaluronidase required fasciotomies.[118,119,321] One case with warm compresses had bullae formation, but necrosis was prevented.[322]
Diazepam	Warm[58]	Warm or cold[13] Cold[46]	Diazepam and phenytoin co-extravasation: necrosis and surgery despite alternating hot and cold compresses for 3 days.[323]
Digoxin	Warm[a]	Warm or cold[13] Cold[58]	None available
Etomidate	Warm[a]	Warm or Cold[13]	None available
Immune globulin	Warm[23]		Necrosis despite warm packs[23]
Lorazepam	Warm[a]	Warm or cold[13] Cold[46]	None available
Mannitol	Warm[50]	Warm or cold[13] Cold[56,58]	No necrosis in 1 case of warm compress with hyaluronidase and 1 case of cold compress with hyaluronidase.[129,324]
Nafcillin	Warm[50]	Warm or cold[13] Cold[46]	Necrosis despite warm compresses.[135]
Parenteral nutrition	Warm[50]	Warm or cold[13,58] Cold[46,56]	Necrosis in 4 cases despite cold compresses in 2 cases, and warm compresses for co-extravasations with lipids in 2 cases.[155,167,325]
Phosphate salts	Warm[50]	Warm or cold[13]	None available
Potassium chloride	Warm[50,58]	Warm or cold[13] Cold[46,56]	20 mEq/L in 5% dextrose and 0.225% sodium chloride: required fasciotomy despite improved edema and discoloration at periphery from use of warm compresses.[326]
Sodium bicarbonate	Warm[50,58,172]	Warm or cold[13] Cold[46,56]	None available
Sodium chloride 3%	Warm[50]	Warm or cold[13] Cold[58]	18 patients had 5 mL purposefully infiltrated: 6 with half normal saline, 6 with normal saline, and 6 with 3% saline. 3 patients in each group were treated with cold compresses and 3 with warm compresses. At 12, 42, and 72 min postinfiltration, the 9 warm compress patients had statistically significantly lower infiltrate volumes versus the 9 cold compress patients.[314]
pH mediated tissue injury			
Acyclovir	Warm[13]	Cold[58]	Cold compresses with gradual recovery over 1 mo.[327]
Amiodarone	Warm[13]	Warm or cold[58] Cold[56]	2 cases (1 observed by an author of this article) with inadequate response to warm compresses where use of hyaluronidase prevented necrosis.[190] One case of necrosis despite cold compresses[328]
Arginine	Warm[13]		2 cases of necrosis despite cold compresses[329,330]
Conivaptan	Warm[13]		None available
Dantrolene	Warm[13]		None available
Doxycycline	Warm[13]	Cold[46]	None available

(*continues*)

TABLE 4

Thermal Compress Recommendations for Noncytotoxic Vesicants (*Continued*)

Vesicant	Thermal compress recommendations		Supportive literature
	Primary	Secondary	
Esmolol	Warm[13]		None available
Gentamicin	Warm[13,48,49,58]		None available
Pentamidine	Warm[13]		None available
Pentobarbital	Warm[13]		None available
Phenobarbital	Warm[13]	Cold[58]	None available
Phenytoin	Warm[13,55]		Fasciotomy prevented with use of dry heat and nitroglycerin patch.[204] Resolution over 3 wk with dry heat and local steroid injection.[220] Necrosis prevented with cold pack, hyaluronidase and saline flush out.[203] Necrosis despite cold compresses and heparinoid cream.[215]
Promethazine	Warm[13]	Cold[46]	Fasciotomy required despite warm compresses[12]
Vancomycin	Warm[13,50]	Cold[56]	None available
Absorption refractory mediated tissue injury			
Lipids	Warm[a]		Injury responded to warm compresses, but inadequate to prevent necrosis.[22]
Propofol	Warm[a]	Cold[58]	Cool packs, no tissue injury. Residual swelling and stiffness for 41 d required physiotherapy, resolution day 62.[28]
Unknown mechanism of tissue injury			
Amphotericin	Warm[a]	Warm or cold[58]	Ice on day 1 then heat and aspirin from day 2 resulting in no necrosis.[227] Necrosis despite local heat, hypertonic wet dressings and oxygen therapy in a co-extravasation with amikacin, dopamine, famotidine, fentanyl, and meropenem.[228]
Metronidazole	Warm[50,58]		None available
Penicillin	Warm[50]	Cold[56]	None available
Valproate	Cold[a]		None available
Vasoconstriction mediated tissue injury			
Dobutamine	Warm[13,46,50,56,58]		Necrosis complicated by cellulitis responded to warm soaks.[331]
Dopamine	Warm[13,46,50,56,58]		2 cases of necrosis despite warm compresses and 1 case of phentolamine with warm compresses without necrosis.[80,241] Warm compresses in 1 co-extravasation with epinephrine resulted in no injury.[247]
Epinephrine	Warm[13,46,50,56,58]		Incidental autoinjector hand exposures with warm compresses: 9 required antidote,[233,254,256,257,261,266,268,271] and 17 cases resolved without antidote administration.[258] Epinephrine applied to skin tear required antidote despite warm soaks.[253]
Methylene blue	Warm[13,58]		None available
Norepinephrine	Warm[13,46,50,56,58]		"Therapeutic application of heat… has not been helpful."[332(p218)] Stellate ganglion block and warm blankets prevented necrosis in a co-extravasation with vasopressin.[292]
Phenylephrine	Warm[13,50,58]		None available
Vasopressin	Warm[13,50]		Necrosis despite warm compresses.[297]

[a]Authors' recommendation.

bacterial infections of damaged tissue have been reported and treated accordingly with topical or systemic antimicrobial agents as indicated.

Saline Flush Out/Irrigation

A highly effective method of physically removing the vesicant is through multiple surgical incisions along with placement of a catheter to administer a physiologic saline flush out and perform aspiration that is similar to liposuction.[41] Saline flush out has become so common in London that advance practice nurses are performing the procedure as opposed to a plastic surgeon.[336] Other variations from this method include open incision and irrigation, incisions and drain insertion, incisions with mechanical

pressure from gentle massage, or saline flush out without aspiration.[13,42,139a,142,167]

Once a wound develops, consultation with a wound care clinician is advisable, because a multitude of different wound care strategies have been reported.[6,9,139a,173,228,323,333,337-340]

DISCUSSION

In the recognition and treatment of an extravasation injury, there are 4 possible outcomes:

- Treatment indicated–treated
- Treatment indicated–untreated: error
- Treatment not indicated–treated: error
- Treatment not indicated–untreated

The potential errors are either overtreatment, if treated without indication, or undertreatment, a lack of treatment when indicated. In the balance of how aggressively an institution manages extravasation injuries, they will tend to overtreat or undertreat extravasations. Because of the unique nature of each extravasation, determining the appropriate level of treatment is challenging. Whether extravasation treatment is indicated is difficult to assess initially. In most reported cases, the extent of injury was far greater than it first appeared. Some common reasons for this are as follows: (1) signs and symptoms occur internally, not just externally where visible; (2) physical signs of damage may be masked by other symptoms; (3) uncertainties in timing and volume of the extravasation; and (4) delayed presentation of symptoms (eg, calcium deposition). Imaging such as x-ray, magnetic resonance imaging, ultrasound, and gallium uptake bone scan (in cases of calcinosis cutis) can be used to estimate the volume of extravasation or the extent of internal injury, but in assessing whether to treat in the absence of compelling evidence either way, the cost of overtreatment or undertreatment must be considered.[61,104,138,160]

Overtreatment of extravasation injury incurs minimal cost, because the antidotes are inexpensive and are well tolerated. Initial undertreatment of extravasation has caused prolonged hospitalization of up to 55 days.[72] The extravasation injury is often more severe than the primary diagnosis. Morbidity and mortality on the magnitude of debridement of necrotic tissue, skin grafting, limb amputation, and even death from fungal meningitis following a parenteral nutrition extravasation have all been reported.[64,162,167,171] Extravasations that appear to be managed appropriately but are undertreated may present later with unforeseen consequences, such as secondary necrotizing fasciitis, limb deformations from prematurely fused growth plates or fibrin deposition, scalp skin grafting with a residual bald spot, an ossified mass inhibiting foot flexion, or retinal detachment from secondary infection.[64,68,341-344] Morbidity can also be accompanied by litigation.[218] Not every extravasation injury requires treatment, but in the decision between potentially committing an overtreatment error versus an undertreatment error, generally the safer decision for the patient and for the clinician is to treat.

For treatment of large-volume infiltrations of medications that are not known vesicants, hyaluronidase should be considered. It has the potential to prevent tissue injury or compartment syndrome as "it can reduce pressure necrosis from mechanical compression of tissues by large amounts of IV fluids trapped in a limited tissue space."[45(p295)] Infiltrations of nonvesicant medications that are large in volume compared with the size of the anatomic infusion site can cause vesicant-like damage. In very low birth weight infants, the line between irritant and vesicant blurs, because most infusion volumes are large compared with their very small size, so large-volume extravasations of any fluid in these patients should be treated with hyaluronidase.[345]

Treatment bias exists in the extravasation body of literature. Less severe extravasations are less likely to receive an antidote but are also more likely to resolve on their own without necrosis, making it appear that antidotes are unnecessary to facilitate healing without necrosis. More severe extravasations are more likely to receive an antidote but are also more likely to result in necrosis or permanent functional deficit, making the antidotes appear ineffective because they were unable to prevent necrosis. The efficacy of an antidote is demonstrated when antidote administration mitigated the catastrophic damage that could have resulted or altogether prevented damage that would have occurred. Because there is no controlled comparator, the damage that might have occurred if not treated can only be presumed based on cases where no antidote was administered. Without standardized severity reporting, appropriately comparing results of antidote-treated cases with untreated cases is difficult if not impossible.

Reporting and observation bias are also seen in extravasation literature. Cases that resolved spontaneously or are similar to previously reported cases are generally not considered worthy of reporting. Alternatively, case series targeting the safety of a peripheral infusion of a vesicant are watching for extravasations to happen and so are likely to catch them earlier, resulting in a low incidence of mild extravasation injuries. This may misrepresent the true incidence and severity of extravasations.

CONCLUSION

Extravasation injury is an established risk of IV vesicant administration. Preventative measures can decrease the risk but not eliminate it, so clinicians should be prepared to treat extravasation injuries in a time-sensitive, evidence-based manner. Treatments are based on the vesicant's mechanism of tissue injury. Cytotoxic vesicants with concentration-dependent toxicity can be treated with warm compresses and hyaluronidase. If the potency of the cytotoxic vesicant cannot be mitigated through dilution, the

most appropriate therapy might be cold compresses with strong consideration of saline flush out. The antidotes for vasopressor extravasations are phentolamine, terbutaline, or nitroglycerin. For pH-mediated, osmolarity-mediated, and absorption refractory extravasations, the antidote is hyaluronidase. Warm compresses should be used for vasopressor, pH-mediated, osmolarity-mediated, and absorption refractory vesicants. Future study regarding absorption refractory vesicants to better characterize this newly proposed mechanism of tissue injury would help clinicians better understand this pattern of tissue damage and could add support to treatment recommendations.

Because the body of extravasation literature is subject to multiple biases, more evidence must be gathered in a standardized way before extravasation recommendations can rely solely on evidence without the need for supporting consensus recommendations. In scenarios similar to extravasation injury where ethical considerations preclude clinical trials, like fetal drug exposure, evidence has been gathered in registries. Registries can be managed by a health system–based research organization, as part of a clinical trial, by a drug manufacturer or joint manufacturer effort potentially as part of a Risk Evaluation and Mitigation Strategy, by a nonprofit research organization or by a professional organization (https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries). The American College of Radiology has a registry for IV contrast extravasation, but no registry covers any other noncytotoxic extravasations (https://www.acr.org/-/media/ACR/Files/Registries/NRDROverview.pdf). According to poison control operatives, poison control advises patients and clinicians on accidental epinephrine autoinjector exposure management and advises clinicians for noncytotoxic extravasations on a regular basis (personal communication, December 3, 2019). When reports of extravasation accumulate, the evidence-based recommendations will become even more robust. Outside of a registry, adverse effects can and should be reported within the United States to the FDA MedWatch. Because the scope of MedWatch contains any serious adverse effect, the required details are not tailored specifically to extravasation injury like a registry reporting form could be. Registry data collected and published by the task force of a professional organization have the greatest chance of producing the requisite case information in the volume necessary to support evidence-based recommendations. The authors hope that as clinicians follow the recommendations contained in this document, the registry could support or refute and refine these recommendations to provide a more robust set of evidence-based noncytotoxic extravasation management recommendations.

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