Development of an Evidence-Based List of Non-Antineoplastic Vesicants

2024 Update

Lisa A. Gorski, MS, RN, HHCNS-BC, CRNI®, FAAN • Jennie Ong, PharmD • Ruth Van Gerpen, MS, RN, APRN-CNS, AOCNS, BC-PMGT • Barb Nickel, APRN-CNS, CCRN, CRNI® • Kathy Kokotis, RN, BS, MBA • Lynn Hadaway, MEd, RN, CRNI®

ABSTRACT

Infiltration of a vesicant, called *extravasation*, can result in severe patient injuries. Recognition of vesicants and their relative risk of injury is essential to extravasation prevention, early recognition, and appropriate treatment. In this article, the Vesicant Task Force (VTF) updates the previously published Infusion Nurses Society (INS) vesicant list from 2017. The 2024 INS list diverges from earlier vesicant lists, such as the 2017 VTF list, by adopting a risk stratification approach based upon documented patient outcomes, in contrast to the reliance on expert consensus or only surrogate risk indicators, such as pH and osmolarity. The methodology used to create the updated list is explained, and the criteria for high- and moderate-risk vesicants and cautionary vesicants are defined.

Key words: extravasation, infiltration, intravenous, necrosis, non-antineoplastic, noncytotoxic, tissue injury, vesicant

Author Affiliations: *Ascension at Home, Brentwood, Tennessee (Gorski); Bryan Medical Center, Lincoln, Nebraska (Ong); Retired from Bryan Medical Center, Lincoln, Nebraska (Van Gerpen); Omaha, Nebraska (Nickel); Retired from BD Medical, Munster, Indiana (Kokotis); Lynn Hadaway Associates, Inc., Milner, Georgia (Hadaway).*

Lisa A. Gorski, MS, RN, HHCNS-BC, CRNI®, FAAN, *served as the Chairperson for the 2017 and 2024 Vesicant Task Force. She has worked for more than 40 years as a clinical nurse specialist (CNS) and educator. She is the author of several books and more than 70 book chapters and journal articles. She is an Infusion Nurses Society (INS) past president (2007-2008), past Chair of the Infusion Nurses Certification Corporation (INCC) Board of Directors, and served as the chair of the INS Standards of Practice Committee for the 2011, 2016, and 2021 editions and Co-Chair for the 2024 Standards. Ms Gorski speaks nationally and internationally on standards development, infusion therapy/vascular access, and home health care.* **Jennie Ong, PharmD,** *has been a clinical pharmacist in the acute care setting for 14 years. Her interests include patient safety, workflow efficiency, and cost containment through order set development, formulary management, and electronic health record optimization. She served on the 2024 INS Standards of Practice Committee for the 2024 Standards as the first and only pharmacist on the committee.* **Ruth Van Gerpen, MS, RN, APRN-CNS, AOCNS, BC-PMGT**, *is a clinical nurse specialist for oncology in Lincoln, Nebraska. A registered nurse (RN) for 45 years, she has over 37 years of experience in oncology and subspecialties in pain management and vascular access. She received her master's degree from Creighton University in Omaha, Nebraska. Ms Van Gerpen has been responsible for education related to cancer, pain management and vascular access, improvement of patient outcomes through implementation of evidence-based practice, and leadership in the development of comprehensive clinical practice standards, programs, and services. In 2020, Dr Ong and Ms Van Gerpen published "Recommendations for Management of Noncytotoxic Vesicant Extravasations," providing an updated list of noncytotoxic vesicants with recommended antidote and compress therapy. She remains active on the local and national levels of the Oncology Nursing Society and continues to peer review and publish.* **Barb Nickel, APRN-CNS, CCRN, CRNI®**, *is a Clinical Nurse Specialist at in a large healthcare system in the US and is responsible for staff development, competency assessment, and process improvement to optimize outcomes in multiple areas of clinical practice, including critical care, infusion therapy, sepsis, and new graduate transition to practice. Ms Nickel has presented nationally on infusion-related topics, is the Chair of the 2024 INS Standard of Practice Committee, and has authored several publications on infusion therapy in the critical care setting. She also serves as Adjunct Research Fellow for Griffith University, Queensland, Australia. She is a consultant and on the speakers' bureau for BD Medical and on the advisory board for Baxter Healthcare.* **Kathy Kokotis, RN, BS, MBA,** *served on the 2017 Vesicant Task Force, has worked as a director of infection control, and has over 30 years of experience in the area of vascular access. Publications include articles addressing cost containment in vascular access and cost losses with peripherally inserted central catheter (PICC) stick and run team, as well as PICC teams. She speaks nationally and internationally addressing PICC programs and decision-making for vascular access. Ms Kokotis is a speaker for APIC, WoCoVa, GaVeCeLT, SIAV, INS, and AVA locally and nationally on PICC programs and vascular access decision-making. She is cocreator of the BD Infusate Consideration Companion and app.* **Lynn Hadaway, MEd, RN, CRNI®**, *has 50 years of experience in infusion nursing and adult education. Her clinical experience comes from infusion therapy teams in multiple acute care settings. She is president of Lynn Hadaway Associates, Inc., an education and consulting company started in 1996. She has authored more than 75 published articles on infusion therapy and vascular access, written 8 textbook chapters on infusion therapy, and is the clinical editor for the book Infusion Therapy Made Incredibly Easy. She served on the INS* Standards of Practice *committees to revise the 2006, 2011, 2016, and 2021 documents and the committees to revise the 2014 and 2022 SHEA Compendium central line-associated bloodstream infection (CLABSI) chapter. She is a past chair of the INCC Board of Directors,*

INTRODUCTION

In 2017, the Infusion Nurses Society (INS) formed a Vesicant Task Force (VTF) with the goal to formulate an evidence-based list of noncytotoxic vesicant medications and solutions. In conclusion of that work, the VTF recommended that the list be re-evaluated on a regular basis as new data emerge and as new medications are introduced into the market.[1] In 2021, a new VTF was formed to review the literature and revise the 2017 vesicant list. Historically, vesicants have been divided into cytotoxic and noncytotoxic vesicants, with cytotoxic vesicants referring to antineoplastic vesicants due to their direct attack on cells that causes damage independent of other factors like pH or osmolarity. Newer evidence has demonstrated that some nonantineoplastic vesicants are cytotoxic, so the list has been retitled to reflect the incorporation of vesicants (including some that are cytotoxic) that are not antineoplastic agents. All vesicants kill cells, so all vesicants could be considered cytotoxic, but cytotoxicity as a mechanism of tissue injury from extravasation refers to vesicants that damage cells in a way that is different from the other recognized methods of injury (pH, osmolarity, vasoconstriction, absorption refractory).

Infiltration of a vesicant, called *extravasation*, can result in severe patient harm and injury, including scarring, permanent functional impairment, chronic pain, and even loss of a limb or digits. Unlike antineoplastic vesicants, nonantineoplastic vesicant administration is ubiquitous, and clinicians often receive no specialized training prior to administration. Patients at heightened risk of extravasation include those with fragile skin and blood vessels (eg, pediatric and geriatric patients) and patients with decreased ability to communicate signs or symptoms of extravasation (eg, impaired cognition, altered mental status, somnolence, language barrier).[2-4] In the course of treating extravasation injuries, hospitalizations may be prolonged, or additional treatment and follow-up visits or hospitalizations may be required. The cost of extravasations is also reflected in litigation, as large compensations for such injuries are awarded.[5] Members of this VTF have been involved in the review of numerous and increasing numbers of malpractice cases involving severe extravasation injuries.

Recognition of vesicants and their relative risk of injury is essential to extravasation prevention, early recognition, and appropriate treatment. As with the previous VTF, the scope of work was limited to development of an updated vesicant list and revising the Extravasation Prevention Checklist (Appendix). Extravasation prevention and early recognition are promoted through vascular access device (VAD) planning, skilled venipuncture techniques, ongoing monitoring, and early recognition and intervention when there are signs and symptoms of potential extravasation. Having a risk-stratified list of identified vesicants can aid health care organizations and clinicians in safely administering vesicants by using the risk level to inform policies and procedures, as well as treatment decisions such as VAD placement and administration monitoring. To the authors' knowledge, there has never been a list of nonantineoplastic vesicants published with evidence-based risk stratification. All previously published lists that stratify vesicants by risk, including the 2017 VTF list, have done so utilizing expert consensus and/or surrogate indicators of risk (eg, pH, osmolarity). This is the first published list of vesicants with risk stratification based on actual patient outcomes.

Notably, treatment is not part of the original or this VTF work. For treatment recommendations, please refer to the extensive review of extravasation treatments authored by 2 current VTF members (Ong and Van Gerpen) published in the *Journal of Infusion Nursing*, and to the 2024 *INS Infusion Therapy Standards of Practice* (*Standards*).[6,7]

Definitions: Vesicants, Irritants, Extravasation, Infiltration

In 2017, the VTF acknowledged the confusion, misunderstanding, and inconsistency among definitions of vesicant, irritant, and extravasation versus infiltration. This remains an issue today. In accordance with the 2024 *Standards*, the definitions are unchanged.[7]

- Vesicant: An agent capable of causing tissue damage when it escapes from the intended vascular pathway into surrounding tissue.
- Irritant: An agent capable of producing discomfort (eg, burning, stinging) or pain as a result of irritation in the internal lumen of the vein with or without immediate external signs of vein inflammation.
- Infiltration: Inadvertent administration of a nonvesicant solution or medication into surrounding tissue, rated by a standard tool or definition.
- Extravasation: Inadvertent infiltration of vesicant solution or medication into surrounding tissue, rated by a standard tool or definition.

INS Member of the Year in 2007, and adjunct associate professor at Griffith University in Queensland, Australia.

Conflicts of interest: *Barb Nickel is on the Advisory Board for Baxter Healthcare; Lisa Gorski receives advisory and speaking honoraria from BD Medical and 3M (Solventum), speaking honoraria from Greiner, and holds stock in IvWatch; Lynn Hadaway was a consultant and speaker for BD Medical and B Braun Medical, and was a consultant for Atrion, AccuVein, and 3M (Solventum). These relevant financial relationships have been mitigated through peer review. There are no other relevant financial relationships for the authors or planners.*

Corresponding Author: *Lisa A. Gorski, MS, RN, HHCNS-BC, CRNI®, FAAN, Ascension at Home, 12403 N. Hawks Glen Ct., Mequon, WI 53097 (lisagorski@hotmail.com).*

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Peripheral Vesicant Administration: Extravasation Risk and Safety Concerns

The administration of vesicants via the peripheral route, whether via a midline catheter (MLC) or a short or long peripheral intravenous catheter (PIVC), is a trend today, yet a trend with considerable risk for extravasation injury. The trend is multifactorial, but 2 contributing factors are (1) the need to treat a condition emergently when a central vascular access device (CVAD) is not available and (2) the emphasis on reduction of CVAD utilization due to concern for CVAD-related complications, especially central line-associated bloodstream infections (CLABSI) and the negative impact of public reporting of these outcomes.[8,9]

While extravasation is a risk with CVADs,[10] the risk is greater with peripheral catheters due to smaller vein diameter and reduced hemodilution, close proximity of endothelial cells that are easily damaged from mechanical and chemical trauma, and flexibility of the extremity in sites commonly chosen for peripheral catheters.[7,11,12] Unfortunately, the rapid escalation in the use of PIVCs to reduce CVAD-related complications has occurred without an accurate evaluation of the impact of this trend on patients and their vessel health and preservation. Several concerns emerge from the current literature on PIVC outcome evaluation, including short and long PIVCs and MLCs, including the variability in PIVC outcome definitions.[13-16] Inadequate education and competency evaluation in accurate and risk-based PIVC assessment and in the recognition and management of PIVC complications has been noted in all phases of nursing preparation, from nursing program curriculum through new hire orientation and beyond.[17-19] In the uncertainty of what to label a PIVC complication, clinicians often document the reason for removal as symptoms (eg, erythema, edema, leaking) rather than designating the actual PIVC complication (eg, phlebitis, extravasation), reducing the accuracy of the patient outcome measurement. In addition, factors such as electronic health record (EHR) limitations and complex nursing workflows contribute to gaps in documentation. It is widely acknowledged that PIVC-related documentation does not convey an accurate picture of insertion, ongoing management, dwell time, infusates administered, or reasons for removal.[17,20,21] Given these substantial limitations and the retrospective nature of the majority of PIVC research studies, a true understanding of the safety profile of peripheral vesicant administration has not been established to the extent that would inform practice.

METHODS

The VTF re-examined the work done to create the 2017 vesicant list, as well as the systematic and narrative literature reviews that had been used to help formulate it.[22-24] A literature search using MEDLINE/PubMed, Cochrane Library, and Google Scholar was performed using the following terms: *extravasation, infiltration, vesicant, noncytotoxic, non-antineoplastic, tissue injury*, and *necrosis*. Literature included case reports, retrospective/prospective studies, and systematic/narrative literature reviews. Narrative and systematic reviews of nonantineoplastic vesicants and drug characteristics were identified and reviewed.[6,25-27] All of the literature was reviewed and discussed by the VTF via regular, ongoing virtual meetings and email communication. Medications were screened for inclusion if they were (1) reviewed and excluded for insufficient data by the 2017 VTF; (2) listed as a vesicant in a review article published after the 2017 VTF review; or (3) listed in the current version of an intravenous (IV) drug handbook AND mentioned the word *extravasation*.[28]

Screening of an infusate for potential inclusion on the 2024 VTF list consisted of gathering information regarding the infusate until there was sufficient evidence either to determine which list it belonged on or to exclude it from the lists. Information regarding pertinent reported adverse effects, special administration instructions, or warnings/precautions were gathered from prescribing information, an IV drug handbook, and drug information databases (including Lexicomp and Micromedex).[28] Reported cases cited in review articles were retrieved and analyzed. Individual literature searches and reviews were performed for individual purported vesicants to identify additional cases of injury or evidence supporting a proposed mechanism of tissue injury (eg, cytotoxicity). The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) was also queried to search for information related to human adverse events reported to the FDA. Only submissions by health care providers were deemed reliable enough to cite as evidence. In an attempt to elucidate which risk level they belong in, epinephrine, methylene blue, phenylephrine, digoxin, and vasopressin were selected for review of FAERS data due to a lack of detailed published cases.

Data regarding a potential mechanism of tissue injury, including physiochemical properties, such as pH and osmolarity, were sourced primarily from Trissel's™ 2 Clinical Pharmaceutics Database,[29] with additional information gathered from prescribing information and published articles. Wherever possible, the pH and osmolarity are reported for the drug in its administrable formulation(s). The administrable formulations (recommended concentration and diluent) were selected according to an IV drug handbook, prescribing information, and drug databases. While, theoretically, the pH of the administrable formulation could be calculated based on a reported pH of a different formulation, the product composition is not described in enough detail to accurately perform such calculations. When the pH of the administrable formulation was unavailable, an alternative known pH was reported (eg, of a more concentrated formulation).

Minimum osmolarity was calculated from the concentrations, molecular weights, and dissociation constants of the drug, diluent, and any excipients (added ingredients for

drug stability) with reported quantities. Dissociation refers to the tendency for a molecule of a drug to separate into multiple molecules when dissolved, such as NaCl into Na+ and Cl-. The presence of excipients may be unaccounted for in the calculation, making the calculated osmolarity a minimum estimation of the administrable osmolarity. To avoid overestimation of the osmolarity, as noted by Poderós et al,[30] calculations were only performed if the dissociation constants are relatively independent of pH or concentration.

Categorization of the 2024 Vesicant List

Many extravasations result in temporary or permanent aesthetic defects. However, to identify the vesicants most likely to cause life-changing injuries from extravasation, the VTF defined *high-risk vesicants* based upon reports of causing permanent functional deficits. A single case of permanent functional deficit could be coincidental, but multiple cases indicate a propensity for causing severe injury. The VTF defined *high risk* as having 2 or more reported cases of permanent functional deficit. Moderate-risk vesicants meet the minimum criteria to be defined a vesicant but are likely not as dangerous as high-risk vesicants. In order to substantiate that the injury was a result of the infusate rather than case-specific factors (eg, large volume infiltration of a nonvesicant), vesicants are classified as *moderate risk* if there are 2 or more cases of injury, or if there is a single case of injury along with a documented mechanism of injury. Cautionary risk infusates may or may not be vesicants. This category contains theoretical vesicants (based on physiochemical properties). Until extravasation injury occurs in vivo, their vesicant status will remain theoretical. Infusates also fall in the cautionary list when injury has occurred, but why (confounding factors such as large volume infiltrations or co-extravasations) or how (ie, mechanism) the injury occurred does not clearly substantiate that the infusate is a vesicant. The criteria for each risk category are summarized in Table 1.

TABLE 1

Summary of Risk Categories

High Risk
• 2 or more published cases with evidence of permanent functional impairment (eg, permanent nerve damage, loss of limb, inability to work or perform activities of daily living)
Moderate Risk
• At least 1 documented case of injury (eg, blistering, necrosis) AND a valid proposed mechanism of tissue injury up to and including a single case of permanent functional impairment OR
• 2 or more documented cases of injury (eg, blistering, necrosis) even without a documented mechanism of tissue injury OR
• Drug prescribing information includes verbiage indicating reports of "extravasation" AND "necrosis"
Cautionary Risk
• Single report of extravasation injury (eg, blistering, necrosis) without a documented mechanism of tissue injury OR
• A documented mechanism of tissue injury (eg, extreme hyperosmolarity) without any reported cases of extravasation injury OR
• Case reports of extravasation injury are unclear or confounded (eg, coadministration with another vesicant)

Literature Review and Vesicant Screening Results

There were many more infusates screened than were included in the vesicant list. Only the most notable exclusions are discussed.

The 2017 VTF described the exclusion of 17 notable infusates from the final vesicant list due to insufficient evidence. Upon rescreening, including review of more recently published evidence (if any), 1 vesicant (propofol) was categorized as a high-risk vesicant, 2 vesicants (immunoglobulin and sodium thiopental) were categorized as moderate risk, and 10 potential vesicants were added to the cautionary list (aminophylline, amphotericin B, ampicillin, doxycycline, gentamicin, lorazepam, metronidazole, oxacillin, penicillin, valproate sodium). Three of the infusates excluded from the 2017 VTF list (albumin, furosemide, morphine) were also excluded by the 2024 VTF for ongoing lack of supporting evidence. Acetazolamide had been listed as a vesicant by Clark et al[22] but was excluded from the 2017 VTF list. Upon rescreening, it was categorized as moderate risk.

The work by Ong and Van Gerpen[6] that focused on evidence-based recommendations for treatment of extravasation injury had 9 purported vesicants beyond those reviewed by the 2017 VTF. Upon screening by the 2024 VTF, 1 (methylene blue) was categorized as a high-risk vesicant, 5 (dantrolene, diazepam, esmolol, lipids, sodium phosphate) as moderate-risk vesicants, and 3 were added to the cautionary list (digoxin, etomidate, potassium phosphate). Screening of products available outside the United States that were excluded as being outside the scope of the work of Ong and Van Gerpen led to the inclusion of 2 high-risk vesicants (metaraminol, tetracycline) and 2 moderate-risk vesicants (the higher pH version of tromethamine and flucloxacillin). Ong and Van Gerpen discovered the identity of fluorescein as a vesicant after their publication and, upon screening by the 2024 VTF, it was added to the moderate list.

Manrique-Rodríguez et al[27] performed a study aiming to standardize dilution of IV drugs across the country of Spain. Drug pH, osmolarity, and cytotoxic nature were identified with the intent to provide guidance for VAD selection. A modified Delphi method approach was used involving a multidisciplinary expert team of physicians and pharmacists. They defined vesicants based upon an osmolarity value of

>600 mOsm/L and a pH level <4 or >9. Every infusate they classified as a vesicant had already met inclusion criteria for the cautionary, moderate-, or high-risk 2024 VTF lists.

Shibata et al[26] reviewed case reports, animal studies, and drug package inserts in an effort to distinguish among vesicants, irritants, and nonirritants. An infusate was classified as a vesicant if the package insert mentioned necrosis from leaking during administration or if published cases in humans or animal studies demonstrated necrosis at the extravasation site. Infusates classified as vesicants that did not meet inclusion for the 2024 VTF list include furosemide, lansoprazole, hydroxyzine, nicardipine, and 3 medication formulations unavailable in the United States (saccharated ferric oxide [FESIN®], gabexate, nafamostat). The pH ranges of furosemide formulations may vary within a country or between countries. In the United States, the reported pH range for furosemide 10 mg/mL is 8.0 to 9.3, but Shibata et al[26] described furosemide 10 mg/mL as having a pH range of 8.5 to 10.0. With a pH range of 8.0 to 9.3 and an osmolarity of about 290 mOsm/kg, furosemide has no valid mechanism of tissue injury and, therefore, does not meet criteria for inclusion on the cautionary list. The furosemide extravasation case cited by Shibata et al[26] was a case of compartment syndrome (CS), which can occur even with infiltrations of nonvesicant infusates. Lansoprazole injection (not available in the United States) is available internationally as an IV push (pH = 11.0) or an infusion (pH = 9.5 to 10.2).[29] The alkaline pH could result in extravasation injury, but other human data to support its identity as a vesicant are lacking. Hydroxyzine is not a vesicant, as it is only recommended for intramuscular (IM) administration.

Nicardipine, pH 3.7 to 4.7, is a well-documented cause of thrombophlebitis but lacks other indicators to support status as a vesicant.[29] A recent summary of adverse extravasation events reported to the Japanese Adverse Drug Event Report (JADER) listed symptoms from 11 extravasation events associated with nicardipine, but none of the cases reported ulceration or erosion, and only 1 reported necrosis.[31] The other reported symptoms were a lump (n = 6), swelling (n = 4), and erythema (n = 1), all of which could have been a result of thrombophlebitis instead of a vesicant injury. Case details are unavailable, so whether the necrosis case was a result of vesicant-like tissue injury or some other cause (eg, thrombosis) cannot be ascertained.

Stefanos et al[24] updated the 2014 review by Reynolds et al,[25] with particular attention given to peripheral administration of vasopressors and hypertonic saline. Screening the purported vesicants led to including 1 (iron sucrose) in the moderate risk and 4 in the cautionary list (angiotensin II, ganciclovir, magnesium, terlipressin). Infusates reported as vesicants by Stefanos et al[24] that did not meet inclusion criteria for the 2024 VTF list include nicardipine, conivaptan, and nitroglycerin. Conivaptan has an acidic pH at 3.4 to 3.8 but lacks other indicators to support status as a vesicant.[29] Despite the presence of propylene glycol in nitroglycerin formulations, ready-to-administer infusions only have an osmolarity of 465 mOsm/L.[29] Propylene glycol in concentrations of 30 mg/mL has not been associated with injury, but necrosis occurred with concentrations of 416 mg/mL.[26] Because propylene glycol is only a stabilizing agent (not the active ingredient), the concentration contained in products is allowed to vary.

Borgonovo et al[32] collected data about antimicrobial drugs and labeled medications as cautionary or "red flag" based upon the following: a pH <5 or >9, for osmolarity >600 mOsm/L, for reported incidence of thrombophlebitis if infused peripherally, or with vesicant properties. Antimicrobial medications labeled as vesicants included vancomycin, acyclovir, and remdesivir, all included in the VTF moderate list. They also included amphotericin B (including the liposomal formulation), which the VTF placed on the cautionary list due to lack of clarity of the mechanism of tissue injury and unclear reports. In summary, the medications reported by a review article as a vesicant that did not meet inclusion criteria for inclusion on the 2024 VTF list include albumin, conivaptan, furosemide, lansoprazole, morphine, and nicardipine.

In order to catch vesicants not yet identified in published lists, every drug with *extravasation* mentioned in its entry in an IV handbook was screened.[28] As a result, 4 vesicants were added to the moderate list (sodium phenylacetate and sodium benzoate [Ammonul], amobarbital, azithromycin, and methocarbamol), and midazolam was added to the cautionary list. After reviewing each of the purported vesicants for potential inclusion in the 2024 VTF list, the VTF compiled the final list of high-/moderate-risk vesicants and cautionary vesicants, as presented in Tables 2 and 3. This is the first nonantineoplastic vesicant list with risk stratification based on reports of patient injury and outcomes.

Mechanisms of Tissue Injury

Understanding how a vesicant causes injury upon inadvertent extravascular administration can help in (1) identification of vesicants or potential vesicants, (2) evaluation of the relative risks of administration, and (3) guiding extravasation treatment decisions. There are currently 5 identified mechanisms whereby vesicant extravasation causes tissue injury:

1. Nonphysiologic pH
2. Vasoconstriction
3. Osmolarity
4. Absorption refractory
5. Cytotoxicity.

While it is known that certain chemical properties or pharmacologic actions of the infusate can affect the propensity to cause tissue injury, how, when, and why injury occurs is a complex and poorly understood process. A single vesicant can cause injury by a combination of mechanisms (eg, vasopressors that are also acidic), and injury

TABLE 2

Vesicants: Moderate and High Risk

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
Antimicrobials			
Acyclovir	Moderate risk	2 cases with permanent aesthetic defect[33,34]	Alkaline pH 10.4 (7 mg/mL in NS)[22]
Azithromycin	Moderate risk	Blistering and whole arm swelling; healed with remaining hypopigmentation[35]	Cytotoxicity[36]
Flucloxacillin (not available in the United States)	Moderate risk	6 cases of necrosis, which resolved without documented permanent functional deficit[37,38]	Acidic pH 5-7[39]
Nafcillin	Moderate risk	9 cases healed without reported permanent functional deficit, 2 of which had skin grafts: 1 was "cosmetic," and the other covered exposed bone without discussion of long-term results[40-42]	Hyperosmolar Infusion: 485 mOsm/kg (60 mg/mL in NS)[29] IVP: Minimum: 149 mOsm/kg (52.6 mg/mL in SW)[**29] Maximum: 532 mOsm/kg (87 mg/mL in NS)[**29]
Pentamidine	Moderate risk	Large area of necrosis over the hand and forearm with permanent decrease in sensation[43]	Acidic pH 4.3-6.5[22,29] (Diluent and concentration dependent)
Remdesivir	Moderate risk	1 case exhibited swelling, hematoma, and severe blistering and 50% to 60% resolution of swelling at 72 h, long-term results not described; 3 cases with hematoma and 1 case only had pain and swelling.[44-46]	Acidic pH 3-4[32]
Tetracycline (not available in the United States)	**HIGH RISK**	2 cases of permanent functional deficit[47]	Acidic pH 2.6-3.0[48]
Vancomycin	Moderate risk	3 cases in neonates/infants with evidence of blistering, erythema, ulcers, necrosis; 1 case with coinfusion of PN; resolution of injuries with wound treatments in all cases; no reports indicating functional impairment[49-51] 4 cases in adults included reports of painful vesicles, blisters, hyperpigmentation, erythema, edema, necrosis, ulcerated tissue with black eschar[52-55]; no reports indicating functional impairment; improvement reported in all cases 1 case with swelling, pain, and coldness at the wrist, which was identified as extravasation and treatment stopped; admitted to hospital 2 mo later with demarcation with all fingers/palmar surface necrotic; thrombotic artery/vein led to amputation at the wrist; unable to obtain additional details[56] Author's note: Questionable extravasation vs arterial thrombotic clot	Cytotoxicity,[57] acidic pH 3-5[29] (RTA)
Electrolytes/nutrition			
Calcium – all salt forms	**HIGH RISK**	Calcium chloride: 9 cases of permanent functional deficit[47,58-63] Calcium disodium edetate: surgical excision of calcified masses as a result of calcinosis cutis[64] Calcium gluconate: 8 cases of permanent functional deficit[47,65]	Hyperosmolar, precipitation Calcium chloride IVP: 2040 mOsm/L (10% CaCl in SW)[29] Infusion: 572 mOsm/kg (2% CaCl in D5W)[22]

(*continues*)

TABLE 2

Vesicants: Moderate and High Risk (*Continued*)

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
			Calcium gluconate IVP: 680 mOsm/L (10% in SW)[29] Infusion: 308 mOsm/kg (5% in D5W)[22]
Dextrose ≥10%	**HIGH RISK**	10% dextrose: 5 cases permanent functional deficit[63,66] 50% dextrose: authors are aware of more than 3 unpublished cases that resulted in permanent functional deficit	Hyperosmolar 10%: 505 mOsm/L[29] 50%: 2525 mOsm/L[29]
Lipids	Moderate risk	2 cases required skin grafting. Normal function returned within 3 mo in 1 case and, in the other, "the area healed well with no further treatment being required."[37,67]	Absorption refractory[6]
Parenteral nutrition	**HIGH RISK**	6 cases of permanent functional deficit and 1 fatality resulting from the extravasation[38,59,68-72]	Hyperosmolar, pH 4.5-7.0[73]
Potassium chloride • 101-299 mEq/L (10.1-29.9 mEq/100 mL) Note: potassium replacement therapy typically falls in this range.	Moderate risk	"Periodic injections of potassium" of unspecified concentration caused necrosis with scarring[74] The authors are unaware of any published reports that definitively fall within this concentration range, as extravasation reports rarely specify the potassium concentration[6]	Hyperosmolar, cytotoxicity (from localized disruptions of cellular exchange of potassium and sodium) 202-598 mOsm/L (101-299 mEq KCl/L)[29]
• 300 mEq/L (30 mEq/100 mL) and greater Note: this concentration is recommended for central line administration only.	**HIGH RISK**	**Committee consensus:** Permanent functional deficits were not explicitly stated in published reports but likely occurred (eg, decreased muscle strength or flexion) based on the documented injuries and repair procedures Case 1: 73-year-old required partial resection of sternocleidomastoid muscle with subsequent vascularized pectoralis flap after jugular line extravasation[75] Case 2: 57-year-old required skin flap repair; significant scarring remained after 3 mo on the hand, wrist, and forearm[76] Case 3: 65-year-old received skin grafting to repair a lesion measuring approximately 5 x 3 in involving the hand, wrist, and forearm[77]	Hyperosmolar 763 mOsm/L (300 mEq KCl/L in NS)[22]
Sodium bicarbonate • Sodium bicarbonate ≥ 0.5 mEq/mL (≥ 4.2%)	Moderate risk	Case 1: 78-year-old extravasation of 4.2% sodium bicarbonate. Patient refused grafting; "spontaneous healing 6 months." Details of aesthetic or functional impairment unavailable.[78] Case 2: 52-year-old coextravasation of isopreterenol and 200 mmol/L (1.68%) sodium bicarbonate; following chemical debridement, the wound healed by secondary intention over 3 mo with a painful scar[78]	Hyperosmolar 4.2%: 1000 mOsm/L[29]
• Sodium bicarbonate ≥ 1 mEq/mL (≥8.4%)	**HIGH RISK**	8.4%: 3 cases of permanent functional deficit.[78,79]	8.4%: 2000 mOsm/L[29]
Sodium chloride ≥ 3%	Moderate Risk	4 injuries resolved without permanent damage (1 was a coextravasation with propofol)[80,81]	Hyperosmolar 3%: 939 mOsm/kg[22]
Sodium phenylacetate and sodium benzoate (Ammonul)	Moderate Risk	"Administration must be through a central venous catheter. Administration through a peripheral line may cause burns. Extravasation of AMMONUL into the perivenous tissues during high flow bolus infusion may lead to skin necrosis, especially in infants."[82] The authors are aware of an unpublished case of injury from extravasation.	Hyperosmolar ≈ 700 mOsm/L (100 mL Ammonul diluted in 1000 mL D10W, total volume 1100 mL)**[29]

(*continues*)

TABLE 2

Vesicants: Moderate and High Risk (*Continued*)

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
Sodium phosphate	Moderate risk	3 cases of long-term aesthetic deficits as a result of phosphate precipitation[83]	Hyperosmolar, precipitation 15 mmol/250 mL NS: 542 mOsm/L**[29] 30 mmol/250 mL NS: 776 mOsm/L**(Trissel's online) 45 mmol/250 mL NS: 1010 mOsm/L**(Trissel's online)
Tromethamine • THAM solution (pH adjusted to 8.6)	Cautionary risk	No reports of necrosis with pH 8.8 [84]	Alkaline pH 8.6[85]
• Tromethamine (non–pH-adjusted version not available in the United States)	Moderate risk	1 case where severe tissue necrosis led to hand amputation[86]	Alkaline pH 10-11.5[87]
Cardiovascular			
Acetazolamide	Moderate risk	55-year-old; ulceration required 2 plastic surgery repairs with remaining permanent aesthetic defect[88]	Alkaline pH 9-10,[29] hyperosmolar IVP: 860 mOsm/L (100 mg/mL in SW)**[29,89] Infusion: 291-348 mOsm/L (5-10 mg/mL in D5 or NS)[29] 548 mOsm/Kg (25 mg/mL in D5W)[22]
Amiodarone	**HIGH RISK**	2 cases of permanent functional deficit including 1 patient with complex regional pain syndrome (CRPS) and forearm muscle deficiency; second patient with elbow, wrist, and finger contractures[90,91]	Acidic pH 3.8-4.1[29] IVP for cardiac arrest: pH 4.1 (50 mg/mL) Infusion: pH 3.8 (2.4-3.6 mg/mL in D5)[27]
Dobutamine	**HIGH RISK**	2 cases of permanent functional deficit[79,92]	Acidic pH 2.5-5.5[29] Vasoconstriction can occur in exposed extravascular tissue[93]
Dopamine	**HIGH RISK**	4 cases of permanent functional deficit[47,94]	Vasoconstriction
Epinephrine	**HIGH RISK**	2 cases where the patient died of unrelated causes before the extravasation injury resolved, likely permanent functional deficits; 1 case was a coextravasation with metaraminol[47,70]	Vasoconstriction

(*continues*)

TABLE 2

Vesicants: Moderate and High Risk (*Continued*)

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
		A study of vasoactive drug infusions in 558 children transported by a single pediatric critical care transport team; 7 children experienced peripheral tissue injuries – 5 with epinephrine, 2 with dopamine; 3 required plastic surgery consult, and 1 of the 5 receiving epinephrine suffered severe necrosis without lasting injuries[95]	
Esmolol	Moderate risk	"Infusion site reactions include irritation, inflammation, and severe reactions (thrombophlebitis, necrosis, and blistering), in particular when associated with extravasation."[96]	Slightly acidic pH 4.5-5.5 (10-20 mg/mL RTA)[29]
Metaraminol (Aramine) not available in the United States	**HIGH RISK**	2 cases of permanent functional deficit[47,97]	Vasoconstriction
Norepinephrine	**HIGH RISK**	2 cases of permanent functional deficit[98,99]	Vasoconstriction
Phenylephrine	Moderate risk	2 adult cases required skin grafting on the ankle; long-term outcomes not reported[100]; 13 peripheral extravasations (stage 2 or less) were caught early due to close observation and resolved without antidote administration[101,102] Author's note: patient hypoperfusion and phenylephrine's mechanism put patients at increased risk of extravasation injury. Use extreme caution for peripheral administration.	Vasoconstriction
Vasopressin	**HIGH RISK**	Case 1: 37-year-old required metatarsal amputation[103] Case 2: 75-year-old with "extensive" necrosis "along the line of the long saphenous vein to above the knee;" required split thickness skin grafting at day 41, but died of a massive pulmonary embolism 48 h postoperatively[104] Author's note: the extravasation injury and required treatments, including surgical intervention, may have contributed to the patient's risk for pulmonary embolus. Case 3: 72-year-old with triangular necrosis (8 x 6 × 10 cm) at antecubital fossa would have required skin grafting but died of variceal hemorrhage[104] Case 4: 44-year-old. Gangrene of forearm approximately 5 × 2 cm healed by secondary intention by 6 wk[104] Case 5: 68-year-old. Skin and muscle necrosis and cephalic vein thrombosis treated with wide surgical incision. Patient died secondary to hepatic encephalopathy, variceal hemorrhage, and pulmonary infiltrates prior to healing.[103] Case 6: 58-year-old. Gangrene and crepitation from forearm up through shoulder. Patient died prior to surgical debridement. Postmortem examination was denied, so cause of death is uncertain.[209] Author's note: Based on the extent and location of injury, had the patient survived, permanent functional deficit would have occurred. Case 7: 59-year-old; necrosis healed with superficial scarring[105] Case 8: 46-year-old. 8 × 18 cm necrotic lesion of wrist and forearm sloughed at day 21 and healed with scarring by secondary intention[106]	Vasoconstriction

(*continues*)

TABLE 2

Vesicants: Moderate and High Risk (*Continued*)

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
Sedatives, antiepileptics			
Amobarbital	Moderate risk	"Extreme care should be taken to avoid perivascular extravasation or intra-arterial injection. Extravascular injection may cause local tissue damage with subsequent necrosis; consequences of intra-arterial injection may vary from transient pain to gangrene of the limb. Any complaint of pain in the limb warrants stopping the injection."[107]	Alkaline pH 9.6-10.4[29]
Diazepam	Moderate risk	1 case of permanent functional deficit[47]	Hyperosmolar 7775 mOsm/kg (5 mg/mL)[29]
Pentobarbital	Moderate risk	"Extreme care should be taken to avoid perivascular extravasation or intra-arterial injection. Extravascular injection may cause local tissue damage with subsequent necrosis; consequences of intra-arterial injection may vary from transient pain to gangrene of the limb. Any complaint of pain in the limb warrants stopping the injection."[108]	Alkaline pH 9-10.5[29]
Phenobarbital	Moderate risk	Skin grafting without permanent functional deficit[109]	Alkaline pH 9.2-10.2[29] Hyperosmolar IVP, undiluted (65 mg/mL): 9285-15,570 mOsm/kg[29] IVP, diluted (6.5 mg/mL in SWFI): 928-1557 mOsm/kg**3[29]
Phenytoin	**HIGH RISK**	2 published cases of permanent functional deficit; additionally, 29 cases of severe soft tissue injury, including 5 amputations, 4 skin grafts, 1 fasciotomy, and 5 deaths reported to the FDA between 1969 and 1984[110-112]	Alkaline pH 10-12.3,[27,29] Hyperosmolar IVP: 3035-9740 mOsm/kg (50 mg/mL)[29] Infusion: 1046 mOsm/L (5 mg/mL in NS)[27]
Propofol	**HIGH RISK**	Published cases: 2 patients required skin grafting and 1 required surgical debridement without report of permanent functional deficit[113-115] The authors are aware of at least 2 unpublished cases that resulted in permanent functional deficit.	Absorption Refractory[6] Acidic pH (formulation dependent) pH 4.5-6.6 (sodium metabisulfate form)[29] pH 7-8.5 (Diprivan and benzyl alcohol form)[29]
Thiopental (not available in the United States)	Moderate risk	Patient required 3 surgical repair operations with resulting permanent ischemic contracture of forearm and amputation of all fingers[47]	Alkaline pH IVP: pH 10-11 (25 mg/mL)[29] Infusion: pH 7.4 (2-4 mg/mL in D5W or Normosol R)[29]
Other			
Arginine	Moderate risk	3 cases required skin grafting and healed without permanent functional deficit[116-118]	Osmolarity, acidic pH 5-6 (10% in SW)[29] 10% in SW: 950 mOsm/L[29]

(*continues*)

TABLE 2

Vesicants: Moderate and High Risk (*Continued*)

	Extravasation Injury Risk	Case Studies/Supporting Evidence	Mechanism(s) of Tissue Injury
Contrast media	**HIGH RISK**	Moderate extravasation injuries included blistering, persistent firmness, swelling/pain, discrete areas of persistent edema, numbness and inflammation with resolution of signs/symptoms at 2 wk; a single severe injury in an adult resulted in a scar on the dorsum of the hand. A single severe injury in a child resulted in brachial plexopathy with ulnar/median nerve damage; however, 1 y later, there were no noticeable defects.[119] 23 patients experienced extravasation injuries without compartment syndrome that resolved without permanent injury. 1 case of ulceration after low osmolarity iodinated contrast; healed with topical therapy.[120] The majority of contrast media extravasations were a result of compartment syndrome with subsequent fasciotomies as addressed in the text. The authors are aware of unpublished cases resulting in permanent nerve damage.	Hyperosmolar Iodine contrast agents: osmolarity values 290-1551 mOsm/kg[121] Gadolinium-based contrast agents: osmolarity 630-1970 mOsm/kg[121]
Dantrolene (Ryanodex)	Moderate risk	"Tissue necrosis secondary to extravasation has been reported."[122]	Alkaline pH 9.5-10.3[29]
Fluorescein	Moderate risk	1 case of permanent functional deficit and 5 cases with permanent aesthetic deficit (skin grafting required) [123,124]	Alkaline pH 8-9.8[29] Hyperosmolar 10%: 572-858 mOsm/kg[125] 25%: 1800-2200 mOsm/kg[125]
Intravenous immune globulin (IVIG)	Moderate risk	1 case in a 3-month-old with moderate scarring after 4 months of wound treatment[37]; 3 additional citations of IVIG extravasations in infants; however, there were no details about the extent of the extravasation injuries.[38,126,127]	Product-specific acidic pH and hyperosmolarity
Iron sucrose	Moderate risk	Case 1: a large skin lesion of the dorsum of the hand and the forearm required skin flap repair with permanent aesthetic defect[128] Case 2: nerve damage presented 16 mo after iron extravasation[129] The authors are aware of unpublished cases of injury from extravasation	Osmolarity, Alkaline pH 10.5-11.1 (IVP and infusion)[27,29] IVP: 1250 mOsmol/L (20 mg/mL)[29] Infusion: 328-385 mOsm/kg (1-2 mg/mL in NS)[29]
Mannitol ≥20%	Moderate risk	1 case of permanent hypopigmentation and 1 case without permanent defect after surgical aspiration of bullae[130,131]	Hyperosmolar 1110 mOsm/L (20% in SW)[29]
Methylene blue	**HIGH RISK**	2 cases permanent functional deficit, 1 case necrosis and blistering; 1 case swelling and discoloration and resolution with hyaluronidase[132-135]	Acidic pH 3-4.5,[29] Vasoconstriction[136]
Promethazine	**HIGH RISK**	Multiple cases of permanent functional deficit[137-140]	Acidic pH 4.5-5[29]

Abbreviations: D5W, 5% dextrose in water; D10W, 10% dextrose in water; IVP, intravenous push; NS, normal saline; RTA, ready to administer; SW, sterile water.
**Author calculated.

TABLE 3

Vesicants: Cautionary List

	pH	Osmolality/Osmolarity	Potential Tissue Injury Mechanism	Case Studies/Supporting Evidence
Antimicrobials				
Amphotericin B formulations- -conventional 0.1 mg/mL D5 -Liposomal (AmBisome®) 1.4 mg/mL D5 -Lipid complex (Abelcet®) in D5	5.7[29] 5-6[30] 5-5.5[29]	256 mOsm/kg[29] 278 mOsm/L[29] "near isotonicity"[29]	Unknown	Case 1: 7-year-old with stage IV coextravasation of dopamine, amphotericin B (formulation not specified), famotidine, fentanyl, amikacin, meropenem. Complete recovery at day 12.[141] **Authors' Comment:** Injury could be attributed to dopamine, a vesicant. Case 2: 36-year-old. Ice, then heat. 3 d of every 4 h aspirin. Full resolution of symptoms (erythema, gross edema, itching, hardened area). Study authors presumed mechanical compression (250 mL infiltrated) caused the injury rather than the conventional amphotericin B (0.16 mg/mL in D5).[142]
Ampicillin IVP: 100 mg/mL Infusion:10-50 mg/mL NS	8-10[29]	602 mOsm/kg[29] 332-566 mOsm/kg[22,29]	Alkaline, Hyperosmolar	Case 1: term neonate. Day 4 of life. Coextravasation of ampicillin, cefotaxime, and dextrose 10% with quarter normal saline. After 8-10 h of IV administration, extravasation ocurred, resulting in 2 blisters and cool, cyanotic skin. Warm packs and 150 units hyaluronidase. No permanent harm.[143] **Authors' Comment**: Injury could be attributed to dextrose 10%, a vesicant. Case 2: 4-year-old. Co-extravasation of ampicillin (unspecified concentration) and chloramphenicol. Dorsum of hand edema. Fasciotomy revealed extensive venous thrombosis. Heparin drip with temporary improvement, but gangrene set in, then hand amputation. Patient heterozygous for factor V Leiden mutation.[144] **Authors' Comment:** Mechanical compression could have caused the thrombosis in a hypercoagulable patient rather than injury from ampicillin. If the ampicillin was hypertonic, that could have contributed to the progressive swelling.
Doxycycline 1 mg/mL D5	3.5[22]	310 mOsm/kg[29]	Acidic	No reported cases of extravasation injury. "Injection site extravasation" is a reported adverse effect.[145]
Ganciclovir 5 mg/mL in D5W or NS	10.5-10.9[27]	288-302 mOsm/kg[27]	Alkaline	1 case of bullae formation along the course of the vein and edema distal to the IV site following extravasation, which the authors attributed to a localized immunoallergic response. Continued therapy via a central line did not result in further bullae formation.[146] **Authors' Comment:** The presentation of bullae proximal to the IV site along the course of the vein may indicate the damage was not a result of vesicant-like extravasation injury.
Gentamicin IVP: 10 mg/mL Infusion:0.8-2.5 mg/mL in D5 or NS	3-5.5[29] 3-5.5[29]	212 mOsm/kg[29] 262-320 mOsm/kg[29]	Acidic	Case 1: Healed by secondary intention without significant scarring or functional deficit. A pediatric case series without case matched details.[38] Case 2: 2-year-old. Coextravasation with penicillin. Necrosis at 24 h. Partial thickness skin loss healed by secondary intention.[147] Case 3: 41-year-old. Coextravasation with penicillin. Ulceration recovered with scarring.[37] **Authors' Comment**: Details regarding Case 1 were unavailable. In the coextravasations with penicillin, a potential vesicant, the cause of damage is unascertainable.

(*continues*)

TABLE 3

Vesicants: Cautionary List (*Continued*)

	pH	Osmolality/Osmolarity	Potential Tissue Injury Mechanism	Case Studies/Supporting Evidence
Metronidazole 5 mg/mL RTA	4.5-7[29]	310 mOsm/L[29]	Slightly acidic	Case 1: Hand amputation after failed treatments with aspirin, pentoxyfylline, and nifedipine.[148] Case 2: No treatments utilized. No damage occurred.[149] **Authors' Comment**: Historic unbuffered metronidazole formulation had pH 0.5-2.0. If the product was not buffered prior to administration, that could explain the dramatic damage in 1995 (case 1).[148] Current formulations are buffered and RTA, which could be why no damage occurred in 2017 (case 2).[149] Based on currently available formulations, metronidazole is likely no longer a vesicant.[150]
Oxacillin IVP: 100 mg/mL NS Infusion: 40 mg/mL NS	6-8.5[29]	706 mOsm/kg**[29] 406 mOsm/kg[29]	Hyperosmolar	Necrotic lesion from unspecified concentration healed without report of permanent defect.[151]
Penicillin 60,000 units/mL in NS	5.5-8.5[29]	437 mOsm/kg[29]	Unknown	2 cases of coextravasation with gentamicin.[37,147] **Authors' Comment**: Gentamicin, a potential vesicant, coextravasated in both cases, leaving the cause of damage unascertainable.
Cardiovascular				
Angiotensin II	5.5[29]	-	Vasoconstriction	Likely a vesicant based upon vasoconstriction. No reported cases of extravasation injury.
Digoxin IVP: 0.1 mg/mL	6.8-7.2[29]	5885-9105 mOsm/kg[29]	Hyperosmolar	1-month-old. Dorsum of foot. Coextravasation: daily digoxin and continuous esmolol. Vesicles and ulcerative lesions healed with scarring but without functional deficit. (FAEHRS Case ID 9 619 731) **Authors' Comment**: Injury could be attributed to esmolol, a vesicant. Digoxin is a probable vesicant due to extreme hyperosmolarity, but small adminsitration volume reduces injury risk.
Terlipressin	-	-	Vasoconstriction	Likely a vesicant based upon vasoconstriction. No reported cases of extravasation injury.
Electrolytes/Nutrition				
Magnesium Sulfate 1% D5 RTA 2% D5 RTA 4% SW RTA 8% SW RTA 11.1% SW	3.5-6.5[29]	333 mOsm/L[29] 415 mOsm/L[29] 325 mOsm/L[29] 649 mOsm/L[29] 900 mOsm/L**[29]	Hyperosmolar (formulation dependent)	**Authors' Comment:** No reported cases of extravasation injury. May be a vesicant depending on the osmolarity of the formulation. RTA 1% D5, 2% D5, 4% SW – likely not a vesicant due to approximately physiologic osmolarity. 8% RTA – potentially a vesicant due to hyperosmolarity. At or above 11.1% compounded formulations should only be administered via a central line due to osmolarity of >900 mOsm/L. These formulations are likely a vesicant.
Potassium Chloride 100 mEq/L or less (eg, maintenance IV fluids)	4-8[29]		Acidic, cytotoxic, hyperosmolar	Cases 1-2: D5 0.45% NaCl with 10 mEq/L KCl (426 mOsm/L, pH 3.5-6.5) infiltrated in a 4-month-old and a 6-month-old. Necrosis healed without report of permanent defect.[152]

(*continues*)

TABLE 3

Vesicants: Cautionary List (*Continued*)

	pH	Osmolality/Osmolarity	Potential Tissue Injury Mechanism	Case Studies/Supporting Evidence
				Case 3: 52-year-old. Unspecified fluid with 10 mEq/L KCl. Necrosis with scarring.[153] **Authors' Comment:** Whether potassium contributed to the injuries is unascertainable.
Potassium phosphate 15-45 mmol/ 250 mL NS	6.2-6.8[29]	450-734 mOsm/L**[29]	Precipitation, hyperosmolar	**Authors' Comment**: Sodium phosphate extravasation resulted in damage from phosphate precipitation.[83] Potassium phosphate likely carries a similar risk.
Sedatives, antiepileptics				
Etomidate IVP: 2 mg/mL	4-7[29]	4965 mOsm/L[154]	Hyperosmolar	Additive propylene glycol causes variable hyperosmolarity; no reported cases of extravasation injury.
Lorazepam IVP: 2 mg/mL Infusion: 1 mg/mL	5.7[29]	>2000 mOsm/kg[22] >1000 mOsm/kg**[22]	Hyperosmolar	Additive propylene glycol causes variable hyperosmolarity. No reported cases of extravasation injury. "Care should be taken to determine that any injection will not be intra-arterial and that perivascular extravasation will not take place. In the event that a patient complains of pain during intended intravenous injection of lorazepam injection, the injection should be stopped immediately to determine if intra-arterial injection or perivascular extravasation has taken place."[155]
Midazolam IVP: 5 mg/mL Infusion: 0.625 mg/mL NS	2.9-3.7[29]	385 mOsm/L[29] 259 mOsm/ kg[29]	Acidic	Potentially a vesicant, based upon acidic pH. No reported cases of injury.
Valproate 23 mg/mL NS	7.6[29]	559 mEq/L**[156]	Hyperosmolar, potentially: skin structure toxicity[157]	62-year-old. 500 mg valproate. Immediate swelling and development of large fluid-filled bullae from hand to elbow. Edema and blistering progressed to compartment syndrome. Bullae drained of 300 mL and escharotomies performed. Patient discharged 11 d later from burn unit. No indication of residual scarring or functional limitations.[157]
Other				
Aminophylline IVP: 25 mg/mL	8.6-9[29]	170 mOsm/L[29]	Hypo-osmolar	Administration of hyaluronidase prevented injury.[42]
Methocarbamol	3.5-6[29]	"Very Hypertonic"[29]	Acidic, hyperosmolar	Additive propylene glycol causes variable hyperosmolarity. No reported cases of extravasation injury. "Pain and sloughing at the site of injection" has been reported.[158]

Abbreviations: D5, 5% dextrose in water; D5 0.45% NaCl, dextrose 5% sodium chloride 0.45%; IVP, intravenous push; NS, normal saline, 0.9% sodium chloride; RTA, Ready to administer; SW, sterile water.
**Author calculated (eg, based on reported osmolarity at a different concentration).

has even been reported from vesicants that have pH or osmolarity ranges relatively close to physiologic. Yet-to-be-identified factors, such as interactions between exposed tissues and specific drug or formulation components, likely explain why injury occurs from some infusates and not others.

It is important to recognize that CS can occur with inadvertent extravascular administration of both vesicants and nonvesicants. Hyperosmolarity and absorption refractoriness are some of the physiochemical properties of vesicants that result in blistering and necrosis but also increase the risk of CS. For example, an absorption refractory vesicant, propofol, is associated with causing CS, as is contrast media, which is often hyperosmolar.[15] Since CS can occur from nonvesicant infiltration, extravasation cases with CS were not used as evidence in categorizing the risk level of the vesicant.

Nonphysiologic pH

Normal physiologic pH ranges from 7.35 to 7.45. Tissues exposed to infusates with nonphysiologic pH can sustain injury from unintended acid–base reactions until the acid/base burden has been neutralized.[26,27] A measurement of the reaction burden, which would be proportionate to the damage, is called *titratable reserve*.[24] Unlike pH, titratable reserve is not concentration dependent. Titratable reserve is often unreported, so pH is still commonly used as a surrogate indicator. Because the rate of acid–base reactions is concentration dependent, between 2 concentrations of the same vesicant, the one with the more extreme pH will likely cause irreversible injury faster. Rate and extent of injury are also dependent on other physiochemical properties, so pH and even titratable reserve should not be used to compare relative risks between different vesicants.

Perhaps due to the physiologic bicarbonate buffering system, tissues seem to tolerate acidic (low) pH better than alkaline (high) pH.[25,27,159] Shibata et al[26] used saline solutions at physiologic pH and normal saline solutions adjusted to a pH of 3 and 5 (by addition of hydrochloric acid) as controls to isolate the effect of vasopressors formulated in acidic pH from the effect of pH itself in causing intradermal damage in rats. Exposure to 100 µL intradermally of the neutral or acidic saline solutions resulted in redness but no induration, ulceration, or change in histopathology. This demonstrates the ability of the physiologic buffer to neutralize small amounts of acid to prevent damage. A larger titratable reserve or an infusate with less mobility due to size/solubility would be more likely to overwhelm the local buffering capacity and result in damage. Manrique-Rodríguez et al[27] defined 3 pH levels when considering VAD selection:

- High risk: <4.0 or >9.0
- Moderate risk: 4.0 to 5.0 or 7.5 to 9.0
- Low risk: 5.0 to 7.5; due to the buffering power of plasma, peripheral administration is acceptable.

Vasoconstriction

Extravasation can result in both chemically and mechanically induced vasoconstriction. Chemically induced vasoconstriction occurs either as a result of the pharmacologic action of the vesicant or as a side effect. Mechanically induced vasoconstriction occurs when extravascular pressures exceed intravascular pressures, decreasing or even stopping venous blood flow. This can occur from the pressure of the extravasated infusate in large volume or anatomically trapped extravasations and can be exacerbated by the attraction of fluid from surrounding tissues when hypertonic vesicants extravasate. Vasoconstriction that reduces tissue perfusion can impair cellular oxygen acquisition and waste removal, resulting in cellular death.

Osmolarity

Physiologic osmolarity is approximately 310 mOsm/L. Both hypotonic and hypertonic solutions can cause tissue damage by forcing cellular fluid shifts. Cells exposed to hypotonic solutions will experience water shifting into the cell, which can result in cell rupture. Hemolysis has been reported with exposure to solutions of 112 mOsm/L.[160] When cells are exposed to hypertonic solutions, water will transfer from within the cells into the interstitial space. The cells can then shrivel, impairing their ability to maintain the trans-membrane transportation of nutrients and waste required for the cell to survive. Not only does the pocket of hyperosmolar infusate draw water to it on a cellular level, but it also attracts water on a larger scale from surrounding tissues, leading to swelling and increasing the risk of mechanically induced vasoconstriction and CS.

Shibata et al[26] tested extravasation reactions in rats to a range of mannitol (5%, 10%, 15%, and 20%) and glucose (5%, 10%, 15%, 20%, 25%, 30%, 40%, and 50%) solutions administered as 100 µL intradermally. Their findings demonstrated that, for a particular infusate, the risk of damage increases with increasing osmolarity. However, even at nearly identical osmolarities, the extent of injury was different based on the identity of the vesicant, so osmolarity should not be used to compare relative risk between vesicants. Even between mannitol and glucose that have very similar molecular weights, the degree of injury was greater from mannitol than glucose at nearly identical osmolarities, likely because mannitol does not readily cross cell membranes. Factors beyond osmolarity that could influence risk of injury include molecular size, shape, solubility, physiologic interactions, and ease of transport across membranes or throughout the extravascular space.

There is no established osmolarity cutoff at which the risk of injury from a hyperosmolar vesicant begins. Histopathology of rats exposed to 5% mannitol or glucose (274–278 mOsm/L) demonstrated no change.[26] Tissue exposed to 10% mannitol or glucose (549–555 mOsm/L) displayed signs of tissue damage, including cellular shedding and infiltration of inflammatory cells. Due to the small volume administered (100 µL), induration, ulceration, and necrosis did not occur from 10% mannitol or glucose (1098–1110 mOsm/L) but did occur from 25% glucose (1388 mOsm/L).

Careful thought should guide the selection of vesicant administration concentrations for an organization. Considerations should include manufacturer instructions, osmolarity, volume burden, use of standardized concentrations, and minimizing manipulations of the sterile infusate, especially at the point of care.

Absorption Refractory

In 2020, Ong and Van Gerpen[6] proposed absorption refractoriness as a mechanism of tissue injury. This mechanism is characterized by drugs with insolubilities or a limited ability to be absorbed into the bloodstream, causing them to persist in the extravasated space. Cells surrounded by extravasated lipids or drugs in a lipid carrier may have impaired access to nutrient uptake and waste removal, limiting their ability to survive. An example is the drug propofol, contained in a lipid carrier, which persists in the interstitial space and leads to deep tissue necrosis and sometimes CS. In the 2024 VTF list, this is also the proposed mechanism of tissue injury associated with extravasation of the nutritional administration of lipids. The identification of this previously undescribed mechanism of tissue injury has been well received by the scientific community. The mechanism has been included in subsequent articles, and authors have specifically included propofol and lipids on their vesicant lists.[25,26]

Cytotoxicity

Cytotoxic vesicants interact with cells in a way that prevents cell growth or causes cell death independent of other mechanisms of injury. Research that involved the use of human umbilical cells has determined that several drugs cause direct cellular damage, including vancomycin and azithromycin.[36,57] This research indicated that, for these vesicants, the degree of cytotoxicity appeared to be concentration dependent. These interactions are not yet fully understood, and the interaction could vary from one vesicant to another.

Antimicrobials

Antimicrobials are among the most commonly administered medications. It is important for clinicians to recognize that, in contrast to many of the vesicants on the 2024 VTF list, antimicrobials are often administered in settings other than hospitals, including outpatient, home settings, and skilled nursing care facilities.

Four antimicrobials were added to the 2024 vesicant list. Intravenous tetracycline, not available in the United States, is associated with 2 reports of functional deficit, with a mechanism of tissue injury being its extremely acidic pH. It is the only antimicrobial rated as high risk. Flucloxacillin, also not available in the United States, was associated with necrosis but not with permanent functional deficit in case reports, all in pediatric patients.[37,38] In a review of peripheral IV antimicrobial administration, flucloxacillin was significantly associated with vessel injury, which included either mechanical blockage or infiltration resulting in irritation or cell damage (extravasation).[161] Remdesivir, a newer antiviral drug used in the treatment of COVID-19, is acidic and rated at moderate risk, as it is associated with several reports of swelling, erythema, and blistering upon extravasation.[44,46] Remdesivir extravasations exhibited an interesting pattern of hematoma formation, along with the blistering. The cause of the hematomas could be related to the coagulopathies seen in patients with COVID-19. A single case of azithromycin extravasation in a pediatric patient resulted in an arm that was firm, distended, and cool to the touch, with subsequent development of bullae; after 4 months of localized treatment, complete healing occurred.[35]

The 4 antimicrobials from the 2017 list remain on the 2024 list: acyclovir, nafcillin, pentamidine, and vancomycin. As a widely used antibiotic across all care settings, vancomycin always generates concern and discussion among infusion clinicians, with frequent informal reporting of extravasations. Because published reports indicate healing after the extravasation event with no permanent functional impairment, vancomycin remains on the moderate list. While 1 report described amputation at the wrist after signs and symptoms including pain, swelling, and coldness, there were limited details as to the specific circumstances surrounding the delayed report of extravasation, and the injury appeared to be possibly associated with arterial occlusion versus injury from PIVC insertion.[56] The VTF reached out to the author for more information, but there was no response. In vitro and animal studies document endothelial damage associated with vancomycin.[57,162,163] Endothelial damage was once attributed to an acidic pH, but vancomycin is now recognized as cytotoxic. In an in vitro study on human umbilical vein endothelial cells, cell death was 25% after 24 hours and more than 50% after 72 hours with continuous vancomycin concentration of 2.5 mg/mL; when the concentration was 5 mg/mL, there was 50% cell death at 24 hours and close to 100% cell death at 48 hours.[57] Intermittent versus continuous infusion was associated with significantly reduced risk for damage. A study investigating continuous vancomycin via a long peripheral catheter (described as an 8-cm "mini-midline") was halted when there was evidence of asymptomatic thrombosis at the catheter

tip with each subject as measured by daily ultrasound.[164] While infiltration/extravasation were not reported, as the study was halted, researchers suggest the direct chemical injury of the vein wall by the vancomycin. Recommendations include central administration of vancomycin when the concentration exceeds 5 mg/mL and when administering continuous vancomycin infusions. Notably, in one of the extravasation reports, the concentration was 321 mg/mL.[54]

Electrolytes/Nutrition

Parenteral nutrition (PN) consists of the administration of amino acids, dextrose, or lipids for the purpose of providing caloric intake and to treat or prevent deficiencies in essential amino acids or fatty acids. Dextrose administration for blood sugar management is not considered PN. In neonates who have a very low caloric reserve, timely initiation and continuing administration of PN can be the determining factors for survival. Children and adults have a much greater caloric reserve and, in these patient populations, while PN administration is eventually needed to sustain life and appropriate administration can improve their healing/recovery ability, delaying initiation of PN or holding PN temporarily due to lack of appropriate IV access is rarely life threatening. An osmolarity of 900 mOsm/L is the generally accepted cutoff above which PN administration should be limited to a CVAD, but peripherally administering PN with an osmolarity <900 mOsm/L is not free of risk; it just has less risk than peripherally administering a higher-osmolarity PN. The further from physiologic the PN osmolarity is, the more dangerous it is. Shibata et al[26] found evidence of tissue damage from exposure to 10% dextrose (505 mOsm/L) in rats, and this risk of injury has been confirmed by multiple reported cases of injury in humans from extravasation of dextrose 10%, including permanent functional damage, making dextrose 10% a high-risk vesicant. The continuous or long durations of infusion of PN put the patient at higher risk that an extravasation will occur. Thoughtful decisions balancing the risks and benefits of peripheral PN administration and formulation selection should be made to protect the patient from undue risk.

Electrolyte administration can be an emergent, lifesaving treatment. When extravasation occurs, a localized supratherapeutic exposure can impair normal physiologic processes and damage cells.

In addition to the effects of hypertonicity, localized hyperkalemia from potassium extravasation is cytotoxic, as it disrupts cellular ion transport necessary for cells to survive. Localized hyperkalemia is so dangerous that concentrations ≥300 mEq/L (30 mEq/100 mL) should only be administered via a central line and are rated high-risk vesicants.[165] Damage from peripheral administration of potassium replacement is not uncommon, and concentrations between 101 and 299 mEq/L (10.1–29.9 mEq/100 mL) have been rated moderate risk. The lower threshold at which potassium no longer poses a vesicant-like risk of injury is unknown, so potassium concentrations at ≤100 mEq/L (10 mEq/100 mL) have been included on the cautionary list. The typical cellular concentration of potassium is 150 mEq/L, whereas normal serum (extracellular) levels range from 3.5 to 5.0 mEq/L.[166]

Localized supratherapeutic exposure to an electrolyte from extravasation can also result in concentrations exceeding the solubility threshold, resulting in precipitation. Calcinosis cutis is the phenomenon where calcium phosphate precipitation deposits in skin and soft tissues. This has been reported both with extravasation of calcium and with extravasation of sodium phosphate and is likely possible with extravasation of potassium phosphate.

Tromethamine is a buffering agent administered for the treatment of acidosis. Injury has occurred from extravasation of the manufacturer's product that has a pH of 10.0 to 11.5. This version was available previously in the United States and is still available internationally. The newer tromethamine product, THAM, is adjusted to a pH of 8.8 and has not been reported to cause extravasation injury. So, the extravasation risk rating for tromethamine is product specific. The product with pH 10.0 to 11.5 is a moderate-risk vesicant, and the product with pH 8.8 is on the cautionary list.

Cardiovascular/Vasopressors

The VTF renamed this section to include vasopressors, as well as other cardiovascular drugs. New to this 2024 list are metaraminol (not available in the United States) and acetazolamide.

Vasopressors are well-known vesicants, with the majority of these medications listed as high risk based on published evidence of patient injuries. This is due to their vasoconstrictive mechanism of action, often in a clinical setting of significant hypoperfusion, necessitating careful VAD selection and maintenance. Phenylephrine is the only vasopressor listed as moderate risk based on the VTF definitions and a lack of published evidence. However, the lack of case study reports may be due to the complexity of the medication regimen in high-acuity patients, making recognition and designation of the true source of extravasation difficult. While angiotensin II and terlipressin are listed as vesicants in at least 1 review,[25] there are no published reports of injuries, and the drug prescribing information does not report extravasation as an adverse event. These drugs have been added to the cautionary list (Table 2). The VTF recommends significant caution with all vasopressors and encourages publication of case reports to build the body of knowledge for these medications.

Vasopressors: Peripheral Administration Issues

There is a growing body of evidence demonstrating that vasopressors may be safely administered peripherally, with the effective use of guidelines to prevent or mitigate complications.[167] This is an important transition point in

critical care because it has the potential to further reduce CVAD utilization and the many associated complications, while ensuring that patients receive required therapy in a prompt and safe manner. Based on a 2015 systematic review, the majority of localized tissue damage occurred in continuous vasopressor administration of 6 hours or more, with increased risk of extravasation injury in the hypoperfused patient.[168] The researchers recommended that peripheral administration of vasopressors be limited to less than 2 hours in a PIVC placed proximally (eg, antecubital fossa or external jugular vein).[168] Since this systematic review was published, numerous studies of varied methodologies and quality have explored this practice (Table 4).[169-185]

To reduce extravasation risk, published recommendations include the following specific to peripheral vasopressor administration with general prevention guidelines applicable as well:

- Limiting peripheral vasopressor administration to short duration (eg, less than 24 hours);
- Limiting administration to 1 vasopressor at the lowest concentration in a peripheral site;
- Ensuring patency and adequate hemodilution around the VAD at insertion (ie, catheter-to-vein ratio), as vasopressors may have both irritant and vesicant qualities;
- Prompt transition to a new VAD if leakage at the site is noted or patency can no longer be validated.[7]

With an identified protocol that is consistently implemented, short-term (eg, 24 hours or less) peripheral administration of vasopressors is a strategy that may reduce CVAD utilization with reported low rates of complications.[184] An additional safety factor is the *Infusion Therapy Standards of Practice* (the *Standards*) recommendation to use a well-placed, patent short PIVC for time-sensitive medications, such as vasopressors, to enhance site assessment and early recognition of complications. The *Standards* and other national and international guidelines recommend that the MLC should not be used for continuous vesicant therapy, such as vasopressors.[7,186-188] This is due to the increased depth of the catheter, difficulty assessing patency with frequent and early loss of blood return, high frequency of reported MLC occlusion-related complications, absence of standardized assessment guidance for deep PIVCs (eg, ultrasound-guided long, MLC), and the potential for more extensive tissue damage should an extravasation occur.[7]

Despite the recommendations stated in national and international guidelines, a recent practice trend is the use of the MLC for continuous and, at times, extended vasopressor therapy.[170,179] While this can be viewed as a natural progression of current clinical practices, particularly in the United States, the pervasive lack of effective monitoring of related outcomes and the lack of high-quality evidence to guide this practice gives cause for concern. Because of the lack of high-quality evidence in support of vasopressor administration using the MLC, the VTF continues to support the avoidance of this practice and to support the above recommendation for short-term, time-critical infusions via the short PIVC before transition to a CVAD. The VTF also recommends that facilities interested in use of the MLC for vasopressor administration initiate the practice within the construct of a well-designed prospective research study to contribute to the body of knowledge in this critical area of practice. Due to VTF concern over this increased use of MLCs, members of the VTF developed a separate review paper to explore the differing definitions of MLC tip placement, risks/considerations, and complications relative to intermittent versus continuous infusions, and to better understand outcomes and complications of MLCs.

Sedatives and Antiepileptics

The section of sedatives and antiepileptics is a new category for the 2024 vesicant list. From the 2017 VTF category, "Other Medications/Solutions," pentobarbital and phenobarbital remain on the 2024 list as moderate risk and phenytoin as high risk.

Thiopental, only available outside the United States and rated as high risk, has an alkaline pH.[47] Propofol, which is rated as high risk, is an absorption refractory vesicant. Propofol is highly lipophilic, and formulations currently available in the United States are made in a lipid carrier made of soybean oil and egg phospholipids. An alternative formulation available outside the United States consists of a triglyceride lipid carrier. Other low-lipid or nonlipid formulations of propofol are being studied. Due to the lipophilic nature of the drug, as well as the lipid carrier solution, propofol seems particularly prone to causing necrosis and CS due to its limited ability to disperse in the tissues and be absorbed into the bloodstream.[6] In addition to the 6 extravasation cases listed in Table 1, there are also 3 published reports of CS requiring fasciotomy with no resulting functional deficits.[189-191]

Other Vesicants

Fluorescein, a drug given IV push for diagnostic eye examinations, is an alkaline drug with high osmolarity and is rated at moderate risk. Despite necrosis from administration being well documented as early as 1980, because of the niche administration setting, it had not been recognized as a vesicant on most published lists.[123,124] Intravenous immunoglobulin (IVIg) was reviewed previously but not included in the 2017 list due to limited citations. Upon rescreening, it is now added to the 2024 moderate list. IVIg is an acidic and often hyperosmolar heterogenous collection of antibodies. There are several citations reporting IVIg extravasation injury, notably all in infants.[126,127] In 1 case, a 3-month-old infant sustained moderate scarring after 4 months of wound treatment.[37] It is important to recognize that there are many IVIg formulations and that specific manufacturer information should be reviewed for osmolarity and pH data.

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
Munroe et al[169] (2023)	Retrospective cohort study SOE V "How are peripheral vasopressors initiated in routine practice and what impact does initiation route have on patient outcomes?" (page 2)	594 adult patients hospitalized with sepsis in 29 hospitals who received vasopressors within 6 hours of arrival	Assessed route of early vasopressor initiation, factors/outcomes with peripheral administration, and central line placement progression. Peripheral administration via the midline, intraosseous, or unknown route were uncommon and were excluded from the study.	Peripheral administration used in 67.3% of patients; with faster initiation of vasopressor with peripheral compared to CVAD route (median 2.5 h vs 2.7 h from hospital arrival, $P = .002$) with no association to in-hospital mortality. Less norepinephrine given peripherally than centrally (84.3% vs 96.8%) with unclear factors. Study noted wide variation in practice, not associated with patient case mix or existence of a facility vasopressor policy; suggests "that additional standardization may be needed." (page 1)
Gershengorn et al[170] (2023)	Cohort study SOE V To evaluate safety outcomes following vasopressor administration through a midline	Vasopressor administration in the following patients: 287 with midlines, 1660 with PICCs, and 884 with midlines who received vasopressors through a separate VAD	Prospective collection of patient data, but design and outcomes were developed after data collection (assessed at 30 days from catheter placement, death, or the time of catheter removal). Analysis included mixed effects logistic regression models to evaluate the independent associations in the 3 population groups.	Lower frequency of catheter-related complications in patients with midlines used compared to PICCs used for vasopressors (5.2% vs. 13.4%, $P < .001$). "Midlines used for vasopressors were associated with greater risk of systemic thromboembolism (vs PICCs with vasopressors: (aOR 2.69 [1.31,5.49], $P = .008$; vs midlines with vasopressors elsewhere: aOR 2.42 [1.29,4.54], $P = .008$)." (page 4)
Abrar et al[171] (2022)	Prospective observational study SOE IV To report the use and outcomes of peripheral vasopressor medications in a PICU in a resource-limited setting (Pakistan)	Children aged 1 mo to 18 y admitted to PICU; 369 patients receiving peripheral vasopressor, majority had sepsis with or without septic shock or respiratory illness	Prospective observation of peripheral administration; protocol developed for at least every 4-hour site assessment, 1 vasopressor per site, included in study if received peripheral vasopressor for at least 4 h.	Extravasation observed in 8 patients (2.2%). Vasopressor used epinephrine, norepinephrine, milrinone, dopamine. Conversion to central line occurred in 127 (34.4%). Peripheral vasopressor administration through a PIVC may be a safe option in PICU patients.
Marques et al[172] (2022)	Prospective, observational cohort study SOE IV To evaluate the use of vasopressors administered peripherally, occurrence of extravasation events in LMIC (low middle-income countries) (Rwanda)	64 adult patients receiving peripheral vasopressors for >1 h	Prospective data was collected surrounding peripheral administration, dose, and duration. Insertion was evaluated hourly until the infusion was discontinued. Extravasation injuries were staged, and treatment protocols used promptly. 16- to 20-gauge PIVC used, 31% placed in AC, 43% placed in forearm/hand.	Single vasopressor administration in 89% of cases. Median duration of infusion 19 h (range of 1–451 h), with 2 extravasation events (2.9%) limited to soft tissue swelling (extravasation score of 1 on 1-4 scale) and no treatment required for recovery. Low rate of extravasation indicates peripheral administration of vasopressors may be acceptable for long durations when a CVAD cannot be placed.

(*continues*)

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors (*Continued*)

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
Marti et al[173] (2022)	Retrospective quality improvement SOE V To evaluate safety and feasibility of peripheral administration of vasopressor to reduce or prompt earlier removal of CVAD	129 orders for vasopressors delivered peripherally in 79 patients	Protocol set a limit of 72 consecutive hours for single vasopressor infusion; required presence of brisk blood return from PIVC to continue infusion; site evaluated at 5 min after initiation, then every hour. Signage and tubing labels used to notify health care team of peripheral infusions. No notation of gauge or location of PIVC insertion sites.	3 potential events noted, but not identified as extravasation. One event documented as phlebitis; 2 events noted as "infiltration/skin blanched/edema < 1 inch" (page 3). No events were labeled extravasation in this sample. No description included of progression of the 3 events listed above. Suggests that short-term peripheral administration of select vasopressors is safe and may be used to reduce CVAD placement; planned future retrospective study sufficiently powered.
Groetzinger et al[174] (2021)	Pilot protocol; retrospective review SOE IV To identify complications and requirements for central line in vasopressor administration	1-y period, 87 patients; median age of 65 y	Protocol: • Lower severity of illness • Lower concentration (8 mg/250 mL, max rate 0.5 mcg/kg/min) • Placement of PIVC above elbow, in large vein with ultrasound if possible • Verification and assessment of PIVC site every 2 h • Creation of extravasation kit for rapid treatment Average duration of infusion was 8.7 h (longest duration 68 h); 16- to 20-gauge PIVC used, 44% ultrasound guided, 61% at area of bicep or AC.	44/87 patients did not require CVAD placement. 3/87 patients had minor complication (listed as infiltration, phlebitis, and unknown); all resolved. Norepinephrine can be safely administered peripherally outside of an emergency situation and for sustained infusions, but difficult to draw definitive conclusions from this pilot study.
Haimovich et al[175] (2021)	Retrospective secondary analysis SOE IV To develop a predictive model for CVAD requirement	Single center, use of Medical Information Mart data base for ICU adult patients admitted between 2008 and 2019 17 053 vasopressor courses of delivery included	Identified vasopressor infusion (1 or more vasopressors administered); the course concluded if vasopressors were interrupted for > 24 hours; the study used the first course of vasopressors in an individual patient. Courses were divided into 4 groups: single agent for <6 h, 6-24 h, >24 h, or multiple agents. The data was analyzed to create a predictive model of CVAD requirement.	3807/17 053 (22.3%) were < 6 hours 7952/17 053 (46.6%) were <24 h Courses involving a CVAD: • 80% of single vasopressor course of <6 h • 80.8% of courses <24 h • 90.4% of courses >24 h • 92.6% of courses with multiple agents. Patients who were intubated, had infectious diseases, were admitted through the ED, had renal impairment, had elevated HR/lower mean arterial pressure prior were more likely to require

(*continues*)

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors (*Continued*)

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
				multiple vasopressors and/or pressor use for >24 h and, thus, might require a CVAD. Authors created an app to assist this analysis.
Messina et al[176] (2021)	Retrospective analysis of 2 y of safety reporting and outcome analysis on norepinephrine infusions in the ED SOE IV To assess occurrence of systemic and localized adverse events from norepinephrine infusions; appraised the association between mortality, ED care, and admission severity scores	Two subgroups of patients who received norepinephrine peripherally in the ED: admitted to ICU 2-y period, total of 127 patients receiving norepinephrine via peripheral IV	Nursing and medical documentation reviewed by 2 independent researchers to determine adverse events related to norepinephrine administration for length of duration, adverse events, mortality. Average duration of norepinephrine infusion 15 h; no catheter gauge listed; location at or above the AC or in external jugular.	3.9% of patients had side effects related to norepinephrine: • 1 with documented extravasation • 4 who required early line removal for "unspecified" reasons. Conclusion: peripheral infusion of norepinephrine was associated with low incidence of adverse events requiring discontinuation of line, reduces delays to vasopressor initiation, and can be considered safe for <12 h at low dosages, with specific protocol of line management, patient monitoring, and use of infusion pump.
Nguyen et al[177] (2021)	Observational retrospective cohort study SOE IV To investigate the use and incidence of extravasation in adult patients receiving norepinephrine peripherally	177 patients, single center; median age of 60	Protocol implemented: required an 18 gauge or larger site at or above the antecubital fossa or external jugular vein; max dose of 20 mcg/min with requirement that CVAD be placed as soon as possible. Required every 1-h site assessment, documentation at least every 4 h; symptoms of extravasation and appropriate treatment included in protocol. Median time of infusion 62 min (average of 50 min duration in ED).	4 (4.5%) patients had extravasation and required conservative treatment. Protocol adherence was 68%; 63% located at AC; 58% were 18 gauge; 84% of patients did require CVAD placement.
Owen et al[178] (2022)	Systematic review and meta- analysis SOE I Examined continuous vasopressor infusion through PIVCs in humans, all ages; investigated associated local anatomic adverse events	23 studies: 16 adult studies and 7 children studies Meta-analysis included 11 adult studies with 16 055 patients, primarily in emergency departments or intensive care units	Included studies if cohort, quasi-experimental or RCT design; 18 were cohort studies (most retrospective), 4 were RCTs (all 4 had some to high risk of bias). Length of infusion ranged from 1.3–49.0 h with most being between 12 and 24 h; 16- to 20-gauge PIVCs used (61% 20 gauge); 64% were located proximal to wrist, 27% in hand/wrist.	For adults, the most common vasopressors were, in order: norepinephrine, neo-synephrine, epinephrine, and dopamine. IV gauge was reported as 16-20 gauge with most being 20 gauge; most located proximal to the wrist. • 19 studies reported events • 7 reported resolution without intervention • 4 reported minor treatment • 8 did not mention treatment.

(*continues*)

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors (*Continued*)

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
				Pooled incidence of events in adults was 1.8%; 3.3% in children. Suggestion that, with careful monitoring, administration through PIVC is safe, but further high-quality research is needed to illustrate comparison to risks of CVAD placement.
Prasanna et al[179] (2021)	Retrospective review SOE IV To evaluate the safety of midline insertion and the incidence of adverse events associated with administration of vasopressors with midlines	Total of 248 adult patients received vasopressor infusion through 4 French 20 cm midline peripheral catheter in single center study	Reviewed for catheter placement, patient demographics and clinical status, type of pressor, length of administration, presence of related complications. Average dwell time of midline catheters 14.7 d. Average duration of continuous vasopressor infusion 7.8 d.	Vasopressors used: norepinephrine, epinephrine, vasopressin, phenylephrine, Angiotensin II. Early complications rate 3.6%: 6 CR-BSI, 1 extravasation, 1 thrombophlebitis. Late complication rate 0.8%: 2 midline-associated DVTs. In 168/248, the midline PIVC was the only catheter required for the entire hospital stay.
Stolz et al[180] (2021)	Single-center retrospective observational cohort study SOE IV To determine if there are differences in safety outcomes with vasopressor delivery via peripheral versus CVAD access; to define patient characteristics	212 patients receiving vasopressors over 12 mo	Retrospective chart review to identify vasopressor administration via peripheral only, peripheral and CVAD, and CVAD only. Average duration: • peripheral vasopressor infusion 10.5 h; no location or gauge listed • peripheral transitioning to central 18 h • central line only 25.7 h	Total extravasations 19/212 Total "leakage" 28/212 • 39/212 received pressors via PIVC (had lowest APACHE scores, shortest duration of pressor infusion, with "minor" complications such as extravasation, leakage, and erythema in 41%) • 155/212 received pressors peripherally then centrally with 28% with "minor" complications • 18/212 had pressors via CVAD only • Indicates "acceptable safety profile" for peripheral administration of pressors • Duration of vasopressor infusion not associated with increased risk of complications.
Cape et al[181] (2021)	Single center, prospective observational pilot study SOE: pilot, quality improvement to determine if norepinephrine can be safely administered via PIVC in selected patients to reduce CVAD use	84 patients received low-dose norepinephrine via PIVC; a total of 92 separate administration events	Patients selected based on status and anticipated short-term need for norepinephrine; protocol included PIVC gauge, site, assessment q 2 h. Data reviewed for adverse events, requirement of CVAD Duration of infusion was 5 min to 31 h; 18- to 20-gauge PIVC used, required to have 2 PIVCs in place, at least 2 inches above	Dose limited to 0.2 mcg/kg/min. "Infiltration" occurred in 3/92 patients (3%). No long-term complications resulted. Mean time to infiltration was 2 h and 43 min. 20- gauge catheter in all 3 instances: CVAD not required in 31/92.

(*continues*)

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors (*Continued*)

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
			wrist and not placed in area of flexion; required to have positive blood return.	Results suggest that low dose norepinephrine is safe to administer through PIVC for <24 h using preventative protocol.
Padmana-ban et al[182] (2020)	Single center, consecutive patient observation study SOE IV To assess feasibility and safety of PIVC administration of vasopressor to reduce CVAD use in resource-limited settings (India)	Included PIVC administration of vasopressor; excluded if initiated via CVAD, durations of infusion <1 h, or inability to secure the PIVC 122 patients met criteria	Patients were observed for PIVC characteristics (size, site), vasopressor characteristics (number ordered, dose, concentration); time of transition from PIVC to CVAD; incidence of extravasation. Mean duration of infusion of 9 h; 57% of PIVCs were 18 gauge; 16-22 gauge used; 36% placed in external jugular; also placed in hand, forearm, AC.	Noradrenaline (norepinephrine) was most common vasopressor at dose of 10.6 mcg/min. CVAD placement most commonly due to escalating dose after 4.5 h. "Grade 2" extravasation injury in 1 patient with duration of infusion of 52 h through 20-gauge PIVC, managed conservatively with no sequelae. Conclusion: PIVC administration of vasopressors through PIVC of 18-gauge or larger caliber into external jugular or forearm vein is feasible and safe; need to balance safety with costs/complications of CVAD placement.
Tian et al[183] (2020)	Systematic Review SOE III To assess frequency of adverse events with PIVC delivery of vasopressors	7 studies identified 1382 patients who received peripheral administration of vasopressor	Included studies if RCT, prospective, retrospective cohort or case series studies that included at least 20 participants, that involved peripheral administration of vasopressors and reported incidence of adverse events; 5/7 of the studies were retrospective, mixed methodological quality. Mean duration of infusions 22 h; 18- to 20-gauge PIV used; some studies restricted to upper arm/AC; further locations not listed.	Vasopressors: norepinephrine, phenylephrine, dopamine, metaraminol, vasopressin, epinephrine. 3.4% extravasation rate (35/1382). All extravasations were treated successfully with conservative treatment. Unable to draw conclusion on longer infusions with short duration of infusions.
Tran et al[184] (2020)	Systematic review and meta-analysis SOE II To assess prevalence of complications in PIVC vasopressor infusions	9 studies including 1835 patients, mean age of 63	Studies included if RCT, quasi-RCT, observational prospective or retrospective studies that reviewed peripheral administration of pressors via peripheral IV and related outcomes. 6/9 were retrospective; 1 RCT included. Length of infusion ranged from 9-49 h with a mean of 25 h; 18- to 22-gauge PIVs used (56% were 20 gauge); location not reported by many studies, others listed	There were 122 complications (7%), of which 117 (96%) were minor. 72% of the complications were extravasations; 5 complications were major/thrombosis. Most common IV gauge was 20. Most common vasopressors, in order, were norepinephrine, epinephrine, and neo-synephrine. Infusion of vasopressors through peripheral lines is a safe alternative. Those that

(*continues*)

TABLE 4

Evidence Table: Peripheral IV Administration of Vasopressors (*Continued*)

Authors, Year of Publication	Study Design/Strength of Evidence (SOE) Research Question/Purpose	Sample/Setting	Methodology Duration of Infusion	Results/Conclusions/Comments
			forearm, hand, AC, external jugular, upper arm.	reported safety guidelines had lower prevalence of complications.
Padrone et al[185] (2018)	Quality Improvement Project SOE V To evaluate outcomes related to utilization of protocol for PIVC administration of vasopressors (using a preestablished protocol)	n = 734 with 783 vasopressor administrations via the PIV route	Criteria for inclusion: order required with volume status assessed; maximum of 48-h infusion (up to 72 h w order); only 1 vasopressor in use; PIVC placement in forearm, upper arm or upper leg, not in areas of flexion; 20 gauge or larger catheter, placement performed and/or verified by US; vein diameter at least 4 mm; blood pressure cuff on opposite arm. Staff education on protocol prior to start. Treatment with specific extravasation protocol. Monitoring: site must be labeled to indicate vasopressor infusion, site assessed every 2 h (identified as critical), patency assessed regularly, prompt recognition and notification of provider of abnormalities. Mean duration of infusion of 49 ± 22 h.	Extravasation occurred in 19 of 734 patients (2%) with no tissue injury following the use of the extravasation protocol. Medications: dopamine, phenylephrine, norepinephrine; vasopressin not allowed per PIV route; 13% transitioned to CVAD placement. Summary: Strict adherence to a nurse-driven protocol for peripheral vasopressors can eliminate the need for CVADs, which will reduce incidence of CLABSI and decrease CVAD device utilization, and potentially reduce CVAD-related complications.
Loubani and Green[168] (2015)	Systematic review SOE III To describe published reports of local tissue injury or extravasation during PIVC or CVAD administration, type of vasopressor used, site and duration of infusion	85 studies included, 80 case studies or series, 1 RCT n = 325 adverse events from administration of vasopressors (318 from the PIVC route, 7 from CVAD route).	Included studies: case reports, case series, observational cohorts, RCTs; adult patients who received IV vasopressors by PIVC or CVAD and reported on outcomes of administration. Mean duration of infusion was 55.9 ± 68.1 h. 14- to 24-gauge PIVCs used; 85.3% of those that resulted in local tissue injury event were located distal to antecubital and popliteal fossa.	Most common site was distal to the antecubital or popliteal fossa; 204 PIVC-related local tissue injury events, 114 were extravasations. Adverse events: 179 skin necrosis, 5 tissue necrosis, 20 gangrene; 4.4% related to major disability felt to be major contributing factor in mortality in 2%. Infusions: norepinephrine (80%), dopamine (9%), vasopressin (7%). Summary: In emergency situations, short-term administration (<2 h) via a proximal, well-placed PIVC is unlikely to cause tissue injury.

Abbreviations: AC, antecubital fossa; BP, blood pressure; CLABSI, central line-associated bloodstream infection; CR-BSI, catheter-related bloodstream infection; CVAD, central venous access device; DVT, deep vein thrombosis; ED, emergency department; HR, heart rate; IV, intravenous; NA, not applicable; PICC, peripherally inserted central catheter; PICU, pediatric intensive care unit; PIVC, peripheral intravenous catheter; RCT, randomized controlled trial; US, ultrasound; VAD, vascular access device.

Iron sucrose, an alkaline drug with an elevated osmolarity, is rated at moderate risk. Published reports include 1 case of required skin flap repair with permanent aesthetic defect and 1 case of nerve damage occurring 16 months after iron extravasation.[128,129] While the VTF was unable to identify reported extravasation injuries associated with other iron formulations, a well-known and often permanent adverse reaction with any iron extravasation is staining of the skin.[192] Methylene blue, an acidic drug with additional mechanisms of action of vasoconstriction and cytotoxicity, is rated at high risk, with several reports of necrosis and nerve injuries, as well as a case of CS.[132-134,193]

Contrast Media

The risk of extravasation injury from contrast media is well-recognized, and contrast medium continues to be rated as a high-risk vesicant.[120,121,194,195] Local toxicity is directly proportional to osmolality. Contrast medium includes iodinated agents commonly used for computed tomography (CT) scans and gadolinium-based agents used for magnetic resonance imaging (MRI). There is much variation of osmolality among these agents. Iodinated contrast agents are divided into ionic and nonionic. High osmolality ionic contrast media (HOCM) have greater chemotoxicity, with osmolality as high as 1400 to 1500 mOsm/kg. Low osmolality ionic contrast media (LOCM) are less toxic, with osmolality ranging from 290 to >800 mOsm/kg. While LOCM has much lower osmolality than HOCM, many in this group still have an osmolality high enough to injure tissue upon extravasation. Osmolality of gadolinium agents ranges from 630 to 1970 mOsm/kg, although they have lower rates of extravasation attributed to much lower administered volumes than iodinated contrast agents.[120,121]

Notably, there are multiple reported cases resulting from CS requiring surgical intervention. No permanent functional injuries were reported in any of these cases. The following are some examples of these cases:

- Seven cases of CS in a hand requiring fasciotomy[56,119,196-199];
- One case of CS requiring multiple stab incisions to facilitate drainage[200];
- Three cases of CS of forearm requiring fasciotomy; 1 in a neonate; another in a pediatric patient[201,202];
- Pediatric patient with upper arm extravasation resulting in brachial plexopathy and ulnar and median nerve damage; no noticeable deficits at 1-year follow-up.[119]

Other Potential Vesicants

Radiopharmaceuticals

Radiopharmaceuticals (RPs) are a group of drugs containing radioactive isotopes used in disease diagnosis, staging, treatment, and monitoring of cancers. While providing a listing of the numerous vesicant RPs is beyond the scope of this article, it is important to recognize the risk of extravasations associated with RPs. Most diagnostic nuclear medicine studies and therapeutic infusions are performed by IV administration of RPs. About 90% of RP use is for diagnostic procedures.[203] Studies over the past several years have documented increasing awareness of and frequency of RP extravasations. Extravasation of diagnostic RPs is common, with 3016 extravasation cases identified in 37 publications. Therapeutic use of RPs was associated with a greater risk of severe tissue damage.[204] Not only can extravasation of RPs result in immediate tissue damage, but a unique result of RP extravasation is development of a malignancy as a result of the localized supratherapeutic radiation exposure. Oversight of RPs is covered both by the FDA and by the United States Nuclear Regulatory Commission (NRC). Old NRC policy from 1980 exempted extravasations from reporting requirements due to frequency of occurrence and "inability to avoid them;" however, there is a need to report these events.[205] In a study aimed at estimating and assessing the radiation dose to localized soft tissue, the researchers found that the RP extravasation rate exceeded 10%, surpassing medical event reporting limits.[205] Radiation safety programs should include identification, mitigation, dosimetry, and documentation of significant extravasation events. There is a need for large randomized controlled trials to actively monitor and report RP extravasations.[206] Protocols to prevent RP extravasations, including careful patency assessment, are critical.

Monoclonal Antibodies

There are an increasing number of monoclonal antibodies (Mabs) used in cancer, as well as in the treatment of noncancer conditions in rheumatology and gastroenterology (eg, rheumatoid/psoriatic arthritis, inflammatory bowel disease). In a review article describing the potential use of Mabs in oncology practice, the risk of extravasation was explored.[207] Acknowledging that the risk of necrosis associated with extravasation is less than that of cytotoxic antineoplastic drugs, inflammation can occur. There are a growing number of Mabs, and with increasing use of these agents, the authors emphasize the importance of reporting extravasations from Mabs. The clinician should exercise caution and awareness of potential risk with Mab administration.

The use of Mabs via antibody-drug conjugates is expanding into new areas, including inflammatory disorders, bacterial infections, cardiovascular disease, and kidney failure.[208] In some therapies, the antibodies are conjugated to cytotoxic agents. With increasingly diverse use of these agents, the authors emphasize the importance of awareness of the potential risk and need to report extravasations from Mabs and antibody-drug conjugates.

LIMITATIONS

Ethical considerations preclude the study of extravasation in humans, so data are and always will be limited to animal models and reported human cases. This lack of information

can make it difficult to make accurate evaluations of risk. The evidence-based risk categorization of the 2024 VTF does reflect the reported ability of a vesicant to cause injury and permanent functional harm, but it has built-in biases. The criteria that 2 cases of injury must have occurred in order to qualify as a high-risk vesicant makes it more likely that commonly administered drugs, drugs administered particularly to high-risk patients, or drugs that have been on the market longer will be considered high risk. Permanent functional harm could also be related to the quality of care received, so as prevention, recognition, and treatment of extravasation injuries improve over time, it may be less likely that newer agents will be categorized as high risk. An increase in the number of cases available for review could help clarify relative risks. Clinicians are encouraged to report extravasation injuries to the FDA Adverse Event Reporting System (FAERS: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers).

CONCLUSION

Extravasation prevention begins with health care organizations and applies to any care setting where vesicants are administered. Each health care organization should compile and publicize a list of vesicants administered in their organization. The list should include, at a minimum, any drugs administered from the 2024 VTF high- or moderate-risk list. Careful consideration, balancing patient safety, should be made about whether to also include the cautionary risk infusates. Some institutions may choose to include additional infusates reported in the literature as vesicants or based on internal reports of extravasation injury. Policies and procedures should incorporate measures for extravasation prevention, and health care organizations must provide education and create competency regarding vesicants, ensuring that nurses and other clinicians recognize the following: (1) whether the drug or solution they are administering is a vesicant; (2) the patient and vascular access device-related factors associated with increased risk of extravasation; (3) interventions to reduce extravasation risk; and (4) the importance of frequent, ongoing monitoring for early recognition and treatment of extravasation.

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APPENDIX

Extravasation Prevention Checklist

Health Care Organization:

- Regularly updated organizational policies/protocols for vesicant identification and extravasation prevention and readily available vesicant-specific extravasation treatment recommendations.
- Written list of vesicant medications/solutions; consider inclusion of risk level; vesicant identification at the point of administration is preferable (eg, on the eMAR or product label).
- Standardized compounding formulas that mitigate the vesicant's potential for injury. Administration of vesicant products closer to physiologic pH and osmolarity can reduce the risk of injury.
- Well publicized organizational restrictions regarding vesicant administration based upon the type of vascular access device (eg, central line administration only or no continuous vesicant infusions via a midline); identify restrictions at the point of administration (eg, on the eMAR or product label).
- Initial and ongoing competency assessment and documentation: venipuncture skill, extravasation prevention, and management.
- Standardized process and content in the medical record for documentation of VAD assessments and to facilitate VAD outcome monitoring.
- Extravasation management specific to the vesicants administered by each organization should either be kept on hand, or at minimum, an action plan should be in place for emergently obtaining them (eg, hyaluronidase, dexrazoxane, sodium thiosulfate, phentolamine, terbutaline, nitroglycerin ointment, warm or cold packs).

Pre-Administration Assessment:

- Identify and, whenever possible, avoid potential extravasation risk factors (Table below).

Extravasation Risk Factors: Use this checklist to identify extravasation risk. Develop an appropriate plan of care based upon identified risk(s).

Peripheral Catheters (short, long, midline)	Central Vascular Access Devices (CVADs)
All Peripheral Catheters • Limited vein selection (lymph node dissection, lymphedema, amputation) • Prior treatment with irritating/sclerosing drugs • Previous multiple venipunctures • Small fragile veins • Darker skin color (more difficult to assess for signs of extravasation) • Venous spasms as result of body temperature changes, raised BP, anxiety, pressure changes from infusion • Absence of blood return* before infusion or loss of blood return during infusion • Inability to communicate symptoms (eg, impaired cognition, altered mental status [delirium, drug side effects], somnolence, language barrier, age [pediatric]) • Sensory/motor deficits (eg, neuropathy, neuro-trauma, post-stroke, paralysis) • Inadequate catheter length within the vessel	**All Central Vascular Access Devices** • Absence of blood return from all CVAD lumens before infusion or loss of blood return during infusion • Catheter tip migration outside the venous system or inadequate length at insertion to place all exit ports inside the vessel • Retrograde flow of drug due to fibrin sheath development • Pinch-off syndrome for CVADs placed via subclavian vein • Inability to communicate symptoms (eg, impaired cognition, aphasia, altered mental status [delirium, drug side effects], somnolence, language barrier, age [pediatric])
Short/Long PIVCs • Subcutaneous probing during insertion (short PIVC, traditional landmark technique without use of visualization device) • Site in area of joint flexion • Catheter in situ longer than 24 hours • Inadequate catheter securement • Long PIVC: reduced ability to detect extravasation if located in deep vein	**Implanted Vascular Access Ports:** • Incomplete port needle insertion • Deeply implanted port with a needle too short to be stable • Needle dislodgement from port septum • Failure to secure noncoring needle in port • Separation of catheter from port body • Catheter damage/fracture (eg, pinch-off syndrome) • Loss of /reservoir integrity (eg, hole/crack/coring of septum/ damage to back of "plastic" housing)
Midline Catheters • **Do not use midline catheters for continuous** vesicant infusions due to reduced ability to identify early signs of extravasation.** • Inadequate catheter-to-vein ratio • Midline trimmed from PICC • Tip advanced too far (beyond the level of the axilla)	

*Blood return: blood that is the color and consistency of whole blood (INS SOP 2024).
**Continuous infusion: a controlled method of intravenous administration given over several hours or longer without interruption.

- Assess appropriateness of a short/long PIVC or midline catheter in accordance with evidence-based recommendations for vesicant administration.
- Advocate for early CVAD placement for continuous vesicant infusions and frequent intermittent drug infusions.

Administer vesicants safely through peripheral catheters (short, long, midlines)

- Existing PIVC:
  - Avoid use if existing PIVC site is older than 24 hours, due to potential endothelial damage from previous infusates, and/or if located in an area of flexion.
- New insertion of short PIVC:
  - Choose smooth, pliable, large veins of the forearm for PIVCs.
  - Avoid venipuncture sites on dorsal aspect of hand, all aspects of wrist, antecubital fossa, lower extremity, or in limb with impaired circulation or lymphatic drainage.
  - Use joint stabilization device (ie, arm/hand board) when areas of joint flexion cannot be avoided.
  - Make no more than 2 attempts at insertion of a short PIVC; if unsuccessful, discuss alternative options with prescriber.
  - Avoid placement of a PIVC below (distal to) a recently used site (includes phlebotomy).
  - Use smallest gauge PIVC; ensure 2/3 of the catheter length is intraluminal.
  - Do not use steel needles.
- Review the complexity of the medication regimen (eg, incompatibilities, number of medications, irritant/vesicant properties).
- Avoid use of PIVCs for continuous infusion of vesicant medications except in the case of time-critical infusions of life-saving therapies (eg, vasopressors).
- Advocate for early transition to a CVAD in patients requiring continuous vesicant administration or frequent intermittent infusions of one or more vesicants who are likely to require such therapy for more than 24 hours due to elevated cumulative risk of extravasation injury.
- Review the method of administration; manual IV push from a syringe provides the ability to assess site during the entire injection versus a "piggy-back" infusion.
- Use extreme caution when administering a vesicant through a PIVC with an infusion pump; pumps do not provide any information about the pathway of fluid flow and will likely continue to pump when the fluid is flowing into the subcutaneous tissue.
- Perform a careful assessment of the PIVC.
  - Ensure that the external catheter is not dislodged, ie, evidence of increased amount of exposed catheter.
  - Aspirate for the presence of a blood return from all PIVCs; minimally check prior to the vesicant infusion and after completion of the infusion.
  - In the event of no blood return via a short PIVC, careful assessment of PIVC patency is confirmed with the ability to flush the PIVC without evidence of swelling, pain, erythema, tenderness, and leaking at the site.
  - In the event of no blood return via a midline or long PIVC, do not administer a vesicant because the catheter tip is located in a deep vein and early signs/symptoms of extravasation may not be detected.
- Monitor for signs/symptoms of extravasation.
- Instruct patient/caregiver to immediately report swelling, skin tightness, pain, burning, or any form of discomfort.

Administer vesicants safely via any central vascular access device:

- Ensure patency of all CVAD lumens
  - Aspirate for a blood return before, after, and at regular intervals unless flushing/aspirating the infusion would endanger the patient (eg, vasopressors) and when clinically indicated (eg, frequent pump alarms, suspected catheter malposition).
  - The presence of occlusion (complete inability to infuse/flush or an absence of blood return) should be addressed prior to vesicant administration.
- Monitor for signs/symptoms of extravasation.
- Instruct patient/caregiver to immediately report swelling, skin tightness, pain, burning, or any form of discomfort.

STOP and immediately discontinue infusion with evidence of extravasation:

- **Complaints of pain, tightness, burning, discomfort at or around the insertion site, catheter tip, or entire venous pathway, or any intrathoracic location for a CVAD.**
- **Localized cool skin temperature.**
- **Swelling at or above insertion site or for CVAD, raised area on neck or chest.**
- **New onset of decreased mobility of extremity.**
- **Change in infusion flow quality (gravity infusion) or frequent pump alarms.**
- **Absence of a blood return that is consistent with whole blood (pinkish blood return is a danger sign).**
- **Leakage of fluid at insertion site.**
- **Resistance during fluid administration (eg, during VAD flushing, EID occlusion alarms), or impaired infusion flow quality for gravity infusion.**
- **Redness or blanching is common but does not always occur.**
- **Assess area, disconnect administration set from VAD hub or port needle (if not needed for antidote administration), aspirate fluid from VAD using small syringe, estimate and document volume and identities of extravasated fluids, and follow organizational protocols for additional treatment actions.**
- **Obtain alternate IV access as necessary, preferably in unaffected limb.**

Abbreviations: BP, blood pressure; CVAD, central vascular access device; EID, electronic infusion device; eMar, electronic medication administration record; IV, intravenous; PIVC, peripheral intravenous catheter; VAD, vascular access device.

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