ONS/ASCO Guideline on the Management of Antineoplastic Extravasation

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgement. Guidance may not be applicable to all patients, interventions, diseases or stages of diseases. Guidance is based on review and analysis of relevant literature, and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and 2 (online only) for more.

PURPOSE Extravasation is an uncommon but high-risk adverse event that occurs when an agent with the potential to cause tissue damage leaks out of the intended administration space into the surrounding area. This guideline presents evidence-based side effect management recommendations to support interprofessional teams in decision making to minimize severity or progression of extravasation injury from antineoplastic treatment in individuals with cancer.

METHODS The Oncology Nursing Society and American Society of Clinical Oncology appointed health care professionals and patient representative members to a panel for guideline development focused on antineoplastic vesicants and irritants with vesicant properties. The panel applied GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology and followed the National Academies of Sciences, Engineering, and Medicine criteria for trustworthy guidelines. A systematic review of studies examining outcomes of antineoplastic agent extravasation in adults informed the guideline. The panel assessed the certainty of the evidence using the GRADE approach.

RESULTS The panel agreed on recommendations related to the use of antidotes for antineoplastic vesicants and irritants with vesicant properties, thermal compress application and duration, and early surgical referral or escalation to specialty care for central venous access device extravasation.

RECOMMENDATIONS This guideline summarizes evidence-based interventions for the management of extravasation of antineoplastic vesicants or irritants with vesicant properties to guide clinical care.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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Despite the steady developments of cancer treatment delivered via oral routes, treatment with antineoplastic therapy via the IV route remains the most common delivery method.[1] Extravasation is an uncommon but high-risk adverse event associated with IV therapy that occurs when an agent with the potential to cause tissue damage

leaks from the intended site of venous delivery.[2,3] Extravasation from an IV site can result in pain, swelling, and erythema in the surrounding area.[4] Agent-specific factors affecting the extent of damage include extremes of pH or osmolarity, hypertonic solution, DNA-binding properties, and vasoconstrictive properties of the drug.[5] In severe cases, progression to blistering, sloughing, ulceration, tissue necrosis, and complications may occur. Extravasation injury may impair mobility and function.[4,6-8] For patients receiving IV cancer treatment, the aftereffects of an extravasation can increase the possibility of treatment delays, potentially jeopardizing cancer outcomes.[9]

Antineoplastic agents are categorized as vesicants, irritants with vesicant properties, irritants, and nonvesicants according to the potential for underlying tissue damage.[2,5] Upon leakage outside of the intended space, vesicants and irritants with vesicant properties pose a risk for extravasation injury. Vesicants are further classified as DNA-binding or non–DNA-binding according to the mechanism of injury. DNA-binding vesicants bind to the DNA of healthy cells in the surrounding tissue, causing apoptosis. Upon cell death, the vesicant is dispersed and taken up by healthy adjacent cells, continuing this cascade and potentially causing severe, sustained tissue damage.[2,8] Non–DNA-binding vesicants are metabolized in the tissue and neutralized with less tissue damage and gradual improvement over time.[8] Regardless of the type of vesicant or irritant with vesicant properties, factors such as volume of the extravasate, anatomic location, and other patient-specific variables influence the severity of tissue damage after an extravasation.[10,11] Table 1 includes a list of commonly administered vesicants and irritants with vesicant properties.

TABLE 1. Commonly Used Vesicants and Irritants With Vesicant Properties

Commonly Used Vesicants	
Antineoplastic Agent	**Classification**
Cisplatin with a concentration of 0.5 mg/mL or higher	Alkylating agent (DNA-binding)
Doxorubicin, daunorubicin, epirubicin, idarubicin	Anthracycline (DNA-binding)
Mitomycin C, dactinomycin	Alkylating agents, antitumor antibiotic (DNA-binding)
Trabectedin, lurbinectedin	Alkylating agents (DNA-binding)
Vincristine, vinorelbine, vinblastine	Antimicrotubule agents, vinca alkaloids (non–DNA-binding)

Commonly Used Irritants With Vesicant Properties	
Antineoplastic Agent	**Classification**
Bendamustine, carmustine	Alkylating agents
Cabazitaxel, docetaxel, paclitaxel, albumin-bound paclitaxel	Antimicrotubule agents, taxanes
Carboplatin, cisplatin, oxaliplatin	Alkylating agents, platinum-based
Etoposide	Topoisomerase II inhibitor
Mitoxantrone	Topoisomerase II inhibitor

NOTE. Based on information from the studies by Ajewole et al,[40] Kaland et al,[66] Olsen et al,[8] and Theman et al.[67]

There is no centralized database for antineoplastic extravasation events, and the exact incidence is not known. In the seminal work of Jackson-Rose et al,[4] researchers established a national target benchmark at 0.09% based on a review of 673 extravasation events of 739,812 antineoplastic infusions. Data collection took place at National Cancer Institute (NCI)–designated cancer centers, which might have influenced the incidence rate. Overall, the reported estimates of extravasation occurring with antineoplastic therapy range from 0.01% to 6.5%.[12,13] Although peripheral IV administration poses a higher risk of an extravasation event compared with administration via a central venous access device, reports of extravasations associated with needle malposition in implanted vascular access devices, disconnection or rupture of the device, and catheter tip migration have been documented.[4,10]

Researchers have noted considerable variability in staff understanding, confidence, and individual awareness of guiding policies for management of antineoplastic agent extravasation.[14-16] To ensure that the most appropriate measures are taken as soon as possible after extravasation, the interprofessional team requires sufficient knowledge on the potential early and late side effects and the immediate and long-term management interventions to apply in practice.[17] Improved knowledge of care and follow-up procedures can increase the comfort levels of staff in managing extravasations.[6]

AIMS AND OBJECTIVES

The aim of this guideline is to provide evidence-based management recommendations for the care of IV antineoplastic agent extravasation side effects in adults who are receiving treatment for cancer, minimize the negative sequelae of extravasation for patients with cancer, and provide a standardized approach to care. The target patients of this guideline include adult patients who are receiving antineoplastic treatment for cancer through venous access. The target users of the guideline include oncology health care professionals, patients, researchers, and decision-makers. Policymakers interested in this guideline include individuals and organizations developing local, national, or international protocols with a goal of improving the management of antineoplastic extravasation in adults with cancer. This guideline is applicable in both inpatient and outpatient settings where clinicians may administer antineoplastic treatment. Although extravasation occurs during other routes of antineoplastic administration (eg, hepatic arterial infusion, intraperitoneal, intravesical), the management of these types of events is outside the scope of this guideline. This guideline also does not cover the selection of vascular

access for antineoplastic therapy or prevention of extravasation events.

GUIDELINE DEVELOPMENT METHODS

The Oncology Nursing Society (ONS) vetted and appointed individuals to the ONS and ASCO guideline panel (Appendix Table A1, online only). The membership of the interprofessional panel consisted of oncology nurses at all levels of practice including staff nurses working in oncology infusion clinics, advanced practice nurses including clinical nurse specialists and a nurse practitioner, two medical oncologists, a clinical pharmacist, and a patient representative. The panel was coordinated by the director of guidelines and quality at ONS (C.C.) in collaboration with GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodologists (K.D.G., R.L.M.) and an ASCO senior guideline specialist (K.B.). The guideline was based on a 2025 systematic review.[18] The panel completed work during virtual meetings and a 2-day in-person meeting to review evidence and formulate recommendations.

The panel assessed the certainty in the supporting evidence and graded the recommendations using the GRADE approach.[19] Policies and procedures derived from the Guideline International Network (GIN) McMaster Guideline Development Checklist and the National Academies of Sciences, Engineering, and Medicine (NASEM) criteria for trustworthy guidelines[20,21] guided the guideline development process, including panel formation, management of conflicts of interest, internal and external review, and organizational approval.

All participants provided financial and intellectual disclosures of interest, which were managed according to ONS policies and the recommendations of NASEM and GIN.[20,21] The panel recorded disclosures at the time of appointment and again at the recommendations meeting, and the ONS/ASCO guideline panel had no relevant conflicts of interest (no material interest in any commercial entity with a product that could be affected by the guidelines).

Formulation of Specific Clinical Questions and Determining Outcomes of Interest

The ONS/ASCO guideline panel met remotely to discuss and prioritize clinical questions. Panelists were instructed to identify clinically relevant questions about extravasation, including questions from patients or those reflecting clinical uncertainty about aspects of extravasation care. Questions were formulated into PICO (patient, intervention, comparator, outcome) components. The panel discussed all possible outcomes and prioritized importance for patients and decision making using the GRADE approach.[22] The panel prioritized the comprehensive list of outcomes and determined the following outcomes as critical for clinical decision making across the PICO questions through ranking survey and deliberation: tissue preservation, tissue necrosis, pain, quality of life, delay of cancer treatment secondary to extravasation, hospitalization, length of stay, need for surgical intervention, and adverse events related to extravasation care.

Synthesis of Evidence and Development of Recommendations

The guideline was informed by a systematic review of randomized controlled trials and nonrandomized designs including cohort, cross-sectional, and case-control studies exploring outcomes in adults with extravasation of antineoplastic agents administered through a peripheral IV line or a central access device published within the past 10 years.[18] This systematic review updates a previous systematic review by Harrold et al.[23]

More details about the methods for the systematic reviews can be found in the study by Gibbs et al.[18] Briefly, a comprehensive search of the literature was conducted for each PICO question prioritized by the panel. Reviewers screened titles and abstracts, and full-text records in duplicate. For each of the eligible studies, risk of bias was assessed using either the Risk of Bias in Nonrandomized Studies of Interventions[24] or the Joanna Briggs Institute critical appraisal tool for case series.[25] The evidence was summarized and assessed in GRADE evidence profiles.

The body of evidence across each outcome was assessed based on factors that either decrease or increase one's certainty: risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude of effect, dose–response gradient, or opposing residual confounding.[26,27] In addition to the certainty of evidence, the panel formulated recommendations considering the balance of benefits and harms, patients' values and preferences, resource use, equity, acceptability, and feasibility. For each question, the panel entered judgment into the GRADE Evidence-to-Decision (EtD) framework using the GRADEpro Guideline Development Tool.[28]

Based on the evidence summarized in the EtD framework table, the panel developed clinical recommendations during the 2-day in-person meeting. The panel arrived at consensus for the final recommendations. The panel also discussed the extent of the use of alternative treatment options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus vote based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the guideline panel.

Interpretation of Recommendations

The strength of the recommendations in this guideline is labeled as strong or conditional. Table 2 provides an interpretation of the recommendations by patients, clinicians,

TABLE 2. Interpretation of Strong and Conditional Recommendations

Strength of Recommendation	Wording in the Guideline	Patients	Clinicians	Policymakers	Researchers
Strong	"ONS and ASCO recommend…"	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients and clinicians make decisions consistent with their values and preferences	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of evidence. In such instances, further research may provide important information that alters the recommendations
Conditional	"ONS and ASCO suggest…"	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps

NOTE. Based on information from the studies by Guyatt et al,[27] Guyatt et al,[22] and Guyatt et al.[19]
Abbreviation: ONS, Oncology Nursing Society.

TABLE 3. Summary of Recommendations: ONS/ASCO Guideline on the Management of Antineoplastic Extravasation

Recommendation	Strength of Recommendation	Quality of Evidence
Recommendation 1: In patients with extravasation of irritants with vesicant properties or vesicant antineoplastic agents for all classes in which a pharmacologic antidote exists (note: paclitaxel and docetaxel are addressed separately in Recommendation 2), ONS and ASCO recommend the use of antidotes rather than no antidotes Remark: Given the potential for an extravasation to cause significant morbidity or develop into a life-threatening situation, the guideline panel made a strong recommendation in favor of the use of pharmacologic antidotes, when they exist, rather than no antidote	Strong	Very low
Recommendation 2: In patients with extravasation of paclitaxel or docetaxel, ONS and ASCO suggest the use of antidote rather than no antidote Remark: The studies that informed this recommendation used hyaluronidase as the antidote	Conditional	Very low
Recommendation 3: For patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO suggest use of a thermal compress rather than no compress Remark: Choice of a warm or cold compress is dependent upon the agent that has extravasated	Conditional	Very low
Recommendation 4: For patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO suggest a longer period of compress (repeated application over more than 24 hours) rather than a shorter period of compress (repeated application over 24 hours or less) (conditional recommendation; very low certainty of evidence)	Conditional	Very low
Recommendation 5: For patients with central line extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO suggest surgical referral/escalation of care in addition to conservative management rather than conservative management alone Remark: High-risk populations—such as those receiving DNA-binding vesicants; those with high-volume estimated extravasation; and those with National Cancer Institute Common Terminology Criteria for Adverse Events grade 2 (erythema associated with symptoms such as edema, pain, induration, and phlebitis), grade 3 (ulceration or necrosis; severe tissue damage), or grade 4 (life-threatening consequences) extravasation—may have greater likelihood of benefiting from surgical referral/escalation in care	Conditional	Very low

Abbreviation: ONS, Oncology Nursing Society.

health care policymakers, and researchers. A summary of recommendations is provided in Table 3.

Document Review

Draft recommendations were reviewed and approved by all members of the panel and opened for public comment from January 13 to January 27, 2025. In addition, a targeted peer review was conducted with three clinical experts on infusion therapy and extravasation. The goal of public comment and targeted peer review was to obtain direct feedback on the draft recommendations and feedback to facilitate dissemination of the final guideline. Following public and targeted comments, the document was revised to address pertinent comments and clarify text where needed; however, no changes were made to the recommendations. The guideline was reviewed and approved by the ONS Board of Directors and the ASCO Evidence Based Medicine Committee.

How to Use These Guidelines

ONS Guidelines are intended to assist clinicians in making decisions about treatment interventions for common symptoms experienced by patients with cancer throughout the treatment trajectory and to inform education, identify research gaps, and promote policy and advocacy. They may also be used by patients in collaboration with their health care team. ONS Guidelines are not medical advice and do not replace care by a cancer care clinician. Using a shared decision-making process, clinicians make decisions with patients, including discussion of patients' values and preferences with respect to their current situation. ONS Guidelines may not include all available treatments for an individual patient. Treatments described in the ONS Guidelines may not be appropriate for all patients or in all scenarios. As scientific advances and new evidence become available, these ONS Guidelines may become outdated. ONS will monitor the evidence at least annually or more frequently if needed and plan to update as the evidence warrants. Following these ONS Guidelines does not guarantee improvement or a successful outcome. ONS does not warrant or guarantee any products described. The full ASCO disclaimer is provided in Appendix 1.

Implementation of ONS Guidelines will be facilitated by forthcoming dissemination tools and resources. The use of ONS Guidelines will also be facilitated by the EtD frameworks and summary of findings tables in each section (Data Supplement, online only).

RECOMMENDATIONS, KEY EVIDENCE, AND QUALIFYING STATEMENTS

The ONS/ASCO guideline panel recommendations contain pharmacologic, nonpharmacologic, and care escalation measures. Following each recommendation, a summary of the evidence is provided, along with a description of the benefits and harms considered and the overall certainty of the evidence as considered by the panel members. Additional factors from the EtD tables are then summarized. A final recommendation is presented with panel remarks if

TABLE 4. Antidotes Used for Management of Antineoplastic Extravasation

Antidote	Extravasation Indications	Dosage	Clinical Considerations
Dexrazoxane: cardioprotective agent known to reduce cardiotoxicity from anthracyclines through fusing with free and bound iron, decreasing anthracycline iron complexes; the exact mechanism of action is unknown for preventing tissue damage in anthracycline extravasation. Potential action is through inhibition of topoisomerase II.	Extravasation of anthracycline therapy (doxorubicin, daunorubicin, epirubicin, idarubicin)	IV administration dosed according to body surface area Day 1: 1,000 mg/m^2 once (maximum dose 2,000 mg) Day 2: 1,000 mg/m^2 once (maximum dose 2,000 mg) Day 3: 500 mg/m^2 once (maximum dose 1,000 mg) Administer the day 1 dose as soon as possible after extravasation and within 6 hours Administer the doses approximately 24 hours apart (plus or minus 3 hours) 50% dose reduction is indicated for patients with a creatinine clearance of <40 mL/minute	Use immediately upon reconstitution and within 2 hours Dose is preferably administered in opposite extremity from the extravasation site Remove cool compress on the extravasation site at least 15 minutes before dexrazoxane administration Adverse reactions Nausea and vomiting Elevated alkaline phosphatase Elevated aspartate aminotransferase Injection site pain or reaction including superficial phlebitis Myelosuppression (possibly confounded by associated anthracycline treatment)
Hyaluronidase: endoglycosidase agent that aids in absorption and dispersion of other injected drugs by modification of connective tissue permeability achieved through hydrolysis of hyaluronic acid	Extravasation of vinca alkaloids vincristine, vinorelbine, and vinblastine Extravasation of the microtubule-inhibiting agents paclitaxel and docetaxel	Various formulations exist. Verify product concentrations Example: 150 units/1 mL divided into five 0.2 mL subcutaneous injections injected with a 25-gauge needle around the perimeter of the extravasation site Administer within 3-4 hours of extravasation	Change the needle with each injection Large extravasations may require additional courses of injections; consult pharmacist Adverse reactions Local injection site reaction
Dimethyl sulfoxide (DMSO): organosulfur solvent, free radical scavenger that increases skin permeability and assists in absorption and dispersion of extravasate	Anthracycline extravasation when dexrazoxane is not available or is contraindicated Mitomycin C Mitoxantrone	DMSO (50%–99%) topical preparation applied to the extravasation site every 8 hours daily for 7 days after extravasation; consult the pharmacist for topical preparation percentage available Apply to area twice the size of extravasation	Implement within the first 10-25 minutes of extravasation Do not apply in combination with dexrazoxane Apply to dry skin only Do not cover Adverse reactions Localized burning or irritation Breath odor
Sodium thiosulfate: hypothesized to be a target for alkylation, thereby neutralizing certain alkylating agents with vesicant properties	Extravasation of >20 mL of cisplatin in high concentration (>0.5 mg/mL) Consider in cases of bendamustine extravasation (sodium thiosulfate was previously indicated for mechlorethamine extravasation; bendamustine is a mechlorethamine derivative with postmarketing reports of tissue necrosis)	Administered as 1/6 M solution For sodium thiosulfate 25% solutions, withdraw 1.6 mL and dilute with 8.4 mL of sterile water and withdraw dose into a syringe For sodium thiosulfate 10% solutions, withdraw 4 mL and dilute with 6 mL of sterile water and withdraw dose into a syringe Administer up to 1 mL as 0.1 mL subcutaneous doses around the area of extravasation	Change the needle with each injection After administration, apply ice pack to the affected area for 6-12 hours Adverse reactions Contact dermatitis Local irritation Warmth Hypersensitivity reaction

NOTE. Consult the full prescribing information before use. Based on information from the studies by Ajewole et al[40]; Akorn Inc[41]; American Society of Health-System Pharmacists[42]; Apricus Pharmaceuticals, USA[43]; Bertelli et al[30]; Boschi and Rostagno[44]; Chung et al[45]; Eneh and Lekkala[46]; and Maly et al.[47]

applicable. The EtD framework can be found for each recommendation in the Data Supplement.

Recommendation 1

PICO: Should patients with extravasation of vesicant or irritant with vesicant properties antineoplastic agents receive an antidote rather than no antidote?

In patients with extravasation of irritants with vesicant properties or vesicant antineoplastic agents for all classes in which a pharmacologic antidote exists (note: paclitaxel and docetaxel are addressed separately in Recommendation 2), ONS and ASCO recommend the use of antidotes rather than no antidotes (strong recommendation; very low certainty of evidence).

Remark

Given the potential for an extravasation to cause significant morbidity or develop into a life-threatening situation, the guideline panel made a strong recommendation in favor of

the use of pharmacologic antidotes, when they exist, rather than no antidote.

Summary of Evidence

The systematic review identified 13 studies that addressed this question. Sample sizes ranged from 12 to 169 patients. Evidence on the use of antidotes for extravasation is limited to nonrandomized, uncontrolled, observational studies and case series. Placebo-controlled trials on this topic would be unethical. There is also a lack of comparative data for different antidote strategies. Mouridsen et al[29] consisted of two observational studies evaluating dexrazoxane for the treatment of anthracycline extravasation. Several of the other studies included multiple different antidotes but were administered for extravasations of specific antineoplastic drugs or drug classes.

Benefits

Potential benefits associated with the use of antidotes for management of extravasation of vesicant or irritant with vesicant properties include tissue preservation, avoiding the need for surgical intervention, preventing hospitalization, and preventing delays of future chemotherapy cycles due to extravasation. The outcome of tissue preservation and avoiding the development of necrosis was informed by 10 studies. Development of necrosis ranged from 0% to 8.3% across nine reports of 10 studies.[11,29-36] Surgical intervention in nine reports of 10 studies ranged from 0% to 8.3%.[11,29-31,34,35,37-39] Hospitalization rates due to extravasation ranged from 0% to 50% in three reports of four studies.[29,31,36] Chemotherapy delays due to extravasation ranged from 8% to 33.3% across four studies.[29,37,39]

Harms and Burdens

The panel decided that the potential harms and undesirable effects of antidotes were likely small. Harms associated with antidotes are dependent on the adverse event profiles of specific antidotes indicated for a respective antineoplastic drug class. Table 4 reviews the extravasation indication, dosing, clinical considerations, and adverse effects associated with four agents used as antineoplastic antidotes: dexrazoxane, hyaluronidase, dimethyl sulfoxide (DMSO), and sodium thiosulfate. Dexrazoxane is indicated for anthracycline extravasation and may increase the risk of transaminitis; however, this reaction is typically mild and reversible.[46] Other systemic reactions, such as hematologic toxicity, were reported in Mouridsen et al[29]; however, this may have been secondary to the antineoplastic therapy administered to patients and not clearly secondary to the antidote. Local adverse events including superficial phlebitis and injection site reactions have also been reported with dexrazoxane. Injection site reaction is possible with the use of subcutaneous hyaluronidase.[41] In Bertelli et al,[30] mild local burning (6.6%) and unpleasant breath odor (28.9%) were reported with the use of topical DMSO.

Certainty in the Evidence of Effects

The certainty in the evidence was rated as very low due to concerns with risk of bias, imprecision, and indirectness. Several studies described multiple cointerventions provided along with antidote administration, including compresses and surgical intervention, which may influence the overall outcome.

Other EtD Criteria

There were no studies identified that addressed healthcare resource utilization and cost-effectiveness associated with administering antidotes for an extravasation. Using the PROGRESS-Plus framework[48,49] for potential impacts on equity, there is likely an impact on those individuals living in rural communities, as well as those unhoused, underinsured or without insurance, and with physical constraints. Additionally, there were no studies on the acceptability and feasibility of providing an antidote, but the intervention is likely acceptable to both patients and clinicians and is regularly provided to patients in multiple settings.

Conclusions

Given the potential for an extravasation to develop into a life-threatening situation, the guideline panel made a strong recommendation in favor of the use of an antidote, when one exists, rather than administering no antidotes. The panel acknowledges the very low certainty in the evidence and the limitations that exist in conducting prospective, controlled trials for this treatment-related complication.

Recommendation 2

PICO: Should patients with extravasation of paclitaxel or docetaxel receive an antidote rather than no antidote?

In patients with extravasation of paclitaxel or docetaxel, ONS and ASCO suggest the use of antidote rather than no antidote (conditional recommendation; very low certainty of evidence).

Remark

The studies that informed this recommendation used hyaluronidase as the antidote.

Summary of Evidence

The systematic review identified five studies that addressed the use of antidotes for the management of taxane-related

extravasation. Evidence on the use of antidotes for extravasation of paclitaxel and docetaxel is limited to nonrandomized, uncontrolled, observational studies. All included studies used hyaluronidase as an antidote.

Benefits

The use of an antidote for taxane-related extravasation may have potential benefits similar to use of antidotes with other antineoplastic extravasation, including tissue preservation, avoiding surgical intervention, preventing hospitalization, and preventing delays of future chemotherapy cycles. In the studies included with a subgroup of patients experiencing taxane-related extravasation, development of necrosis ranged from 0% to 8.3% among patients who received an antidote.[11,31,32,35]

Harms and Burdens

The panel found that the potential harms and undesirable effects of antidotes used for a taxane-related extravasation were likely trivial. Antidote-related adverse events were not reported in the studies identified in the systematic review. Hyaluronidase has been associated with the development of local injection site reactions.

Certainty in the Evidence of Effects

The certainty in the evidence was rated as very low due to concerns with risk of bias, imprecision, and indirectness. Although hyaluronidase was used in each study identified, there were several studies that also provided multiple other cointerventions, including DMSO, compresses, and surgical intervention, which may influence the overall outcome.

Other EtD Criteria

There were no studies identified describing how patients value the main outcome, but it can be assumed that patients find tissue preservation important. Although many adverse events with antidotes are reversible, some may find the risks of the antidote and its administration to outweigh the benefits. There is potential for moderate costs with administration of an antidote. No studies were identified for the acceptability and feasibility of providing the antidote, but antidotes are regularly provided in practice with extravasation events.

Conclusions

There is less certainty that an extravasation of paclitaxel or docetaxel will progress to severe, life-threatening sequalae. Therefore, the guideline panel made a conditional recommendation in favor of the use of an antidote rather than administering no antidote in such a clinical scenario. The panel acknowledges the very low certainty in the evidence. Details on hyaluronidase use are included in Table 4.

Recommendation 3

PICO: Should thermal compress versus no compress be used for patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents?

For patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO suggest use of a thermal compress rather than no compress (conditional recommendation; very low certainty of evidence).

Remark

Choice of a warm or cold compress is dependent upon the agent that has extravasated.

Summary of Evidence

Six studies addressing the use of a compress to treat the extravasation of an irritant with vesicant properties or vesicant antineoplastic agent were identified from the systematic review.[30,32,38,50-52] A nonrandomized, observational design was used across all studies.

Benefits

The benefit for use of a compress was determined to be moderate due to the potential for an extravasation to progress to a severe condition without any treatment. Reported benefits associated with use of a compress include tissue preservation, possible avoidance of the need for surgical intervention, and the unlikely occurrence of compress-related adverse events.[30,32,38,50-52] Three studies reported tissue preservation as an outcome, with the occurrence of necrosis ranging from 0% to 14%.[30,32,52] The range for avoidance of the need for surgical intervention was 0%-24% across five studies.[30,38,50-52] Bertelli et al[30] reported no adverse events with intermittent use of a cool compress.

Harms and Burdens

The panel determined that any harm associated with using a compress is trivial. Bertelli et al[30] reported no compress-related adverse events, even when applying local cooling for as long as 60 minutes every 8 hours for 3 days. A financial burden may be imposed on patients in the outpatient setting as they may be expected to purchase compress packs for application at home.

Certainty in the Evidence of Effects

The overall certainty of the evidence was determined to be very low due to risk of bias, imprecision, and indirectness. Several of the studies had multiple cointerventions with compress application, including antidotes and surgical interventions, that may have influenced the overall study outcomes.

Other EtD Criteria

It was determined that the use of a compress is acceptable to key stakeholders and feasible to implement, as compresses are regularly used in practice for many conditions. In the outpatient setting, there is a possibility that important uncertainty about or variability in how much value is placed on using a compress to prevent progression of an extravasation to a severe condition exists. The tradeoff will be the potential progression against time, effort, and resources required to support the frequency of compress use.

Conclusions

For patients with extravasation of an irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO are issuing a conditional recommendation for the use of a compress rather than no use of a compress. The choice of a warm or cold compress would be dependent upon the agent that has extravasated. Cold compresses are indicated to vasoconstrict and reduce the spread of extravasate. Cold compresses are meant to localize the drug to prevent further dispersal into the surrounding tissue and are indicated for extravasations of alkylating agents, anthracyclines, and antimetabolites. Warm compresses are meant to disperse the agents and are indicated for vinca alkaloid, etoposide, oxaliplatin, paclitaxel, and docetaxel (when coadministering hyaluronidase). For extravasation of agents not previously listed with specified cold or warm compress, consider several factors including the mechanism of action of the agent, presence of pain or edema, and patient comfort when deciding which type of compress to apply.

Recommendation 4

PICO: Should a longer duration of thermal compress application versus a shorter duration of thermal compress application be used for patients with extravasation of an antineoplastic vesicant or irritant with vesicant properties?

For patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO suggest a longer period of compress (repeated application over more than 24 hours) rather than a shorter period of compress (repeated application over 24 hours or less) (conditional recommendation; very low certainty of evidence).

Summary of Evidence

Five studies were identified from the systematic review reporting the duration of compress application.[30,32,38,50,51] All five reported a nonrandomized, observational design.

Benefits

The benefit for use of longer duration of compress application (>24 hours) was determined by the panel to be moderate when compared to compresses applied for <24 hours. However, this may be likely affected by the variability with the agent, type of IV line, and severity of the extravasation. Benefits reported in the literature include tissue preservation[30,32] and avoidance of the need for surgical intervention.[30,38,50,51]

Harms and Burdens

The panel decided that any harm from longer duration of compress application compared to shorter duration is trivial based on one study that reported no compress-related adverse effects, even with the application of local cooling for 3 days.[30]

Certainty in the Evidence of Effects

There are serious concerns with risk of bias, imprecision, and indirectness with the included studies. Several studies had multiple cointerventions with the application of compresses, including antidotes and surgical interventions, with both interventions having the potential to influence overall outcomes. Therefore, the panel determined that the overall certainty of the evidence is very low.

Other EtD Criteria

It was determined that the application of a compress is acceptable to key stakeholders and feasible to implement, as compresses are regularly used in practice for many conditions. In the outpatient setting, there is a possibility that important uncertainty about or variability in how much value is placed on using a compress to prevent progression of an extravasation to a severe condition exists. The tradeoff will be a potential progression of the condition against time, effort, and resources required for longer duration of compress use. The panel again noted that a financial burden may be imposed on patients in the outpatient setting, as they may be expected to purchase compress packs for applications at home.

Conclusions

For patients with extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS and ASCO are issuing a conditional recommendation for longer duration (more than 24 hours) of compress application rather than shorter duration (24 hours or less) based on very low certainty of the evidence.

Recommendation 5

PICO: Should surgical referral/escalation of care versus conservative/nonsurgical management be used for patients with central line extravasation of antineoplastic vesicants or irritants with vesicant properties?

For patients with central line extravasation of irritant with vesicant properties or vesicant antineoplastic agents, ONS

and ASCO suggest surgical referral/escalation of care in addition to conservative management rather than conservative management alone (conditional recommendation; very low certainty of evidence).

Remark

High-risk populations—such as those receiving DNA-binding vesicants; those with high-volume estimated extravasation; and those with NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 2 (erythema associated with symptoms such as edema, pain, induration, and phlebitis), grade 3 (ulceration or necrosis; severe tissue damage), or grade 4 (life-threatening consequences) extravasation—may have a greater likelihood of benefiting from surgical referral/escalation in care.

Summary of Evidence

The literature review and recommendations focused only on extravasations involving patients with central lines. A lack of evidence and concerns about resource constraints precluded the panel from including peripheral lines in this recommendation. Surgical referral for peripheral line extravasation may be based on clinical findings, severity of the extravasation, and agent extravasated; clinical judgment should be used to determine whether referral is indicated for peripheral line extravasations.

Outcomes related to central line extravasation included tissue preservation (necrosis), unplanned surgical intervention, hospitalization, surgical/wound care complications, pain, quality of life, and delay of future cancer treatment secondary to extravasation. Two nonrandomized studies discussed surgical referral or escalation of care in patients with extravasation and included 30 patients and 13 patients, respectively.[10,36] Tissue complications and necrosis ranged from 0% to 18% in studies with early surgical referral or intervention in extravasations involving implanted ports.[10,36] In Azaïs et al,[10] extravasated agents included vesicants (51.5%), irritants with and without vesicant properties (45%), and nonvesicants (3%), with 97% of cases undergoing surgery and 87.5% undergoing early surgical lavage including central line removal in 53.1% of those who received early surgical lavage. Six cases were severe and required a second intervention. Of these six cases, four were receiving a vesicant and the other two were receiving oxaliplatin. Only one patient required a skin graft. In 80% of the cases, the total extravasated volume was >50 mL. The main unfavorable outcome predictors were vesicant or vesicant property–classified agents and extravasated volume >50 mL. Steiert et al[36] evaluated subcutaneous washout procedure (SWOP) exclusively without application of antidotes. Extravasated agents included paclitaxel, epirubicin, vinorelbine, docetaxel, carboplatin, and cisplatin. Prolonged tissue induration and residual inflammation were present in 20% of cases and lasted 14 days. The referral time interval between the extravasation injury and the SWOP ranged from 140 minutes to 795 minutes. Results showed no cases of tissue breakdown or serious complications, and the majority reported a decrease in pain after SWOP. There were no hospitalizations reported due to the extravasation or extravasation-related complications.

Benefits

The balance of effects probably favors the surgical referral or escalation of care for extravasation in central lines based on moderate desirable effects, trivial undesirable effects, and probably no variability in values. However, the benefit for surgical referral or escalation of care minimizes the potential for the development of skin ulcerations, necrosis, loss of mobility, and life-threatening consequences associated with untreated extravasation.

Harms and Burdens

No harm from surgical referral or escalation of care was reported in the literature. Increased anxiety and financial burden related to the out-of-pocket or indirect costs of lost time and wages for surgical referral/escalation of care for the patient were identified as potential undesirable anticipated effects. These undesirable anticipated effects could potentially be mitigated by patient education and support services.

Certainty in the Evidence of Effects

The certainty for surgical referral or escalation of care in addition to conservative management rather than conservative management alone was rated as very low certainty of evidence. This rating is based on concerns with risk of bias, inconsistency, indirectness, and imprecision.

Other EtD Criteria

There is no available research discussing how individuals value the main outcomes; the panel felt it can be assumed that individuals consider tissue preservation important to quality of life.

Conclusions

The panel determined that prompt surgical referral or escalation of care may minimize the potential for the development of skin ulcerations, necrosis, loss of mobility, and life-threatening consequences while recognizing patient anxiety and financial burden as potential undesirable anticipated effects of referral. The guideline panel issued a conditional recommendation for surgical referral or escalation of care in addition to conservative management, rather than conservative management alone, for antineoplastic extravasation in a central line.

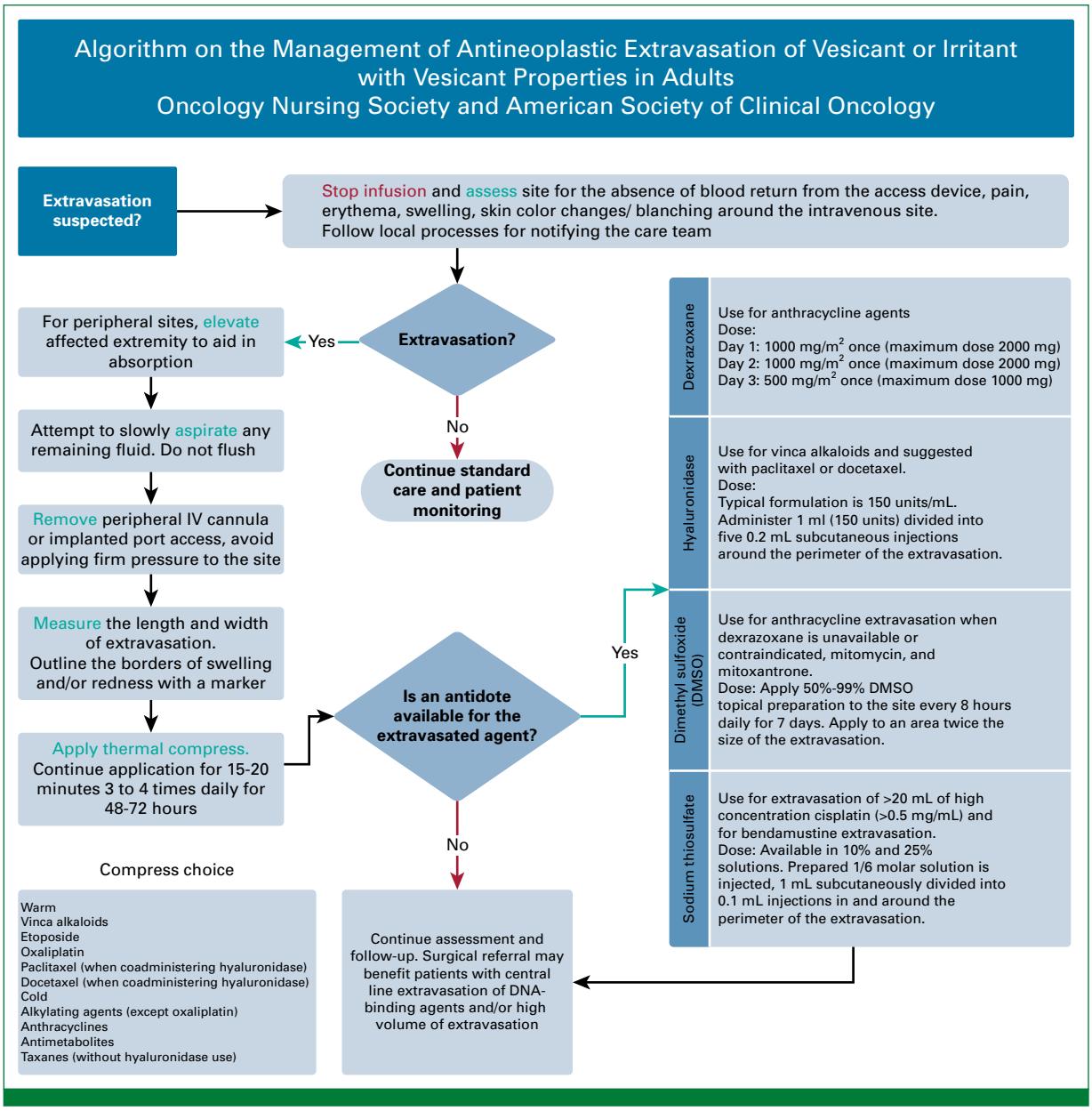

FIG 1. Algorithm on the management of antineoplastic extravasation of vesicant or irritant with vesicant properties in adults.

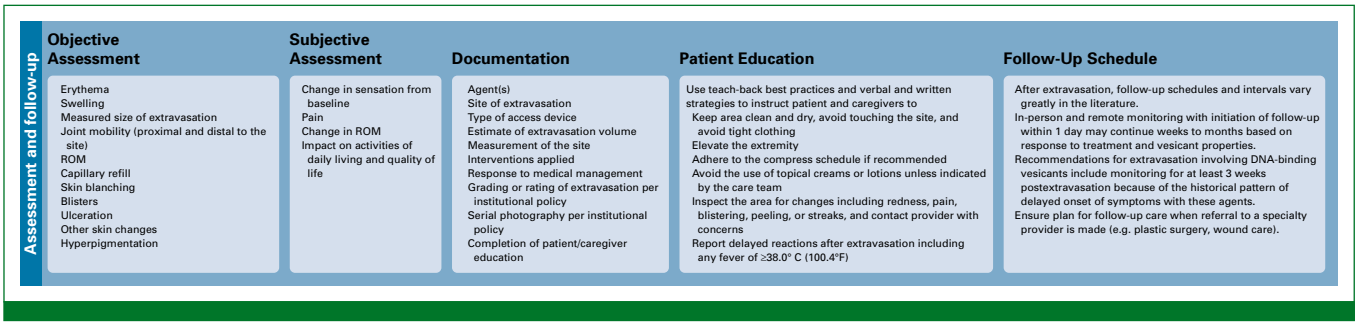

FIG 2. Extravasation assessment and follow-up care. Note. Based on information from the studies by Ener et al, 2004[13]; Ferrari et al, 2016[11]; Langstein et al, 2002[50]; Olsen et al, 2023[8]; and clinical experiences of the Expert Panel. ROM, range of motion.

TABLE 5. National Cancer Institute CTCAE, Version 5.0: Infusion Site Extravasation

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion site extravasation	Painless edema	Erythema with associated symptoms (eg, edema, pain, induration, phlebitis)	Ulceration or necrosis, severe tissue damage, operative intervention indicated	Life-threatening consequences, urgent intervention indicated	Death

NOTE. Extravasation is defined as a disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation, and marked discomfort at the infusion site. Based on information from the National Cancer Institute Cancer Therapy Evaluation Program, 2017.[57]

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

DISCUSSION

To our knowledge, this is the first collaborative guideline on extravasation management between ONS and ASCO. Resources on evidence-based management of extravasation are limited because of the lack of comparative trial data and feasibility in studying this topic. A cooperative guideline was published by the European Society of Medical Oncology (ESMO) and the European Oncology Nursing Society (EONS) in 2012.[53] The ESMO/EONS guideline details prevention measures and patient-specific risk factors covered elsewhere within ONS resources, including *Access Device Guidelines: Recommendations for Nursing Practice and Education*[54] and *Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice*.[8] The ONS/ASCO guideline adds an updated appraisal of literature through 2024, a comprehensive algorithm to guide clinical practice and follow-up, and transparent EtD supplement to capture the depth of the panel discussion on the included questions. Key similarities between guidelines include indications for hyaluronidase for vinca alkaloid and taxane extravasation, dexrazoxane for anthracycline extravasation, and DMSO for mitomycin C extravasation. This ONS/ASCO guideline adds suggestions for use of sodium thiosulfate in extravasation of high-volume (>20 mL), high-concentration (>0.5 mg/mL) cisplatin and in bendamustine extravasation and includes the use of DMSO for mitoxantrone extravasation. Although the ESMO/EONS guideline recommends DMSO 99% concentration, only the 50% preparation is currently available in the United States. The literature that informed this guideline reported DMSO preparations between 50% and 99% concentration.

IMPLICATIONS FOR PRACTICE

According to oncology safety standards, in areas where antineoplastics are dispensed and administered, policy aligned with the current literature is available to guide management of an infiltration or extravasation.[55] Patients may show varying degrees of symptoms with extravasation, and early recognition and management help to improve outcomes.[7,9,56] During routine patient education, reinforcing critical symptoms to report during and after an infusion may mitigate added harm.[5,7,9] Presenting symptoms may include pain, erythema, swelling, and skin color changes or blanching at or around the infusion site. The presence or absence of blood return from the venous access device is assessed. The absence of blood return and pain or swelling around the insertion site indicates an extravasation. Figure 1 shows a support algorithm that details immediate action in the case of an extravasation with a vesicant or an irritant with vesicant properties including the management of the site, the thermal compress choice based on the agent or agent classification, and antidote indications and notes. Figure 2 includes routine follow-up assessment, documentation, and patient education that can be applied throughout extravasation care. A resource combining the treatment algorithm and follow-up assessments is shown in the Data Supplement.

The NCI CTCAE, version 5.0 (Table 5), is available to grade an extravasation using descriptive terminology that translates to a grade on a basic five-point scale ranging from mild symptoms or asymptomatic occurrence to life-threatening consequences.[57] A benefit of incorporating the CTCAE scale for grading an extravasation is the well-established use of the grading system in general oncology practice settings. The scale, however, lacks detailed assessment criteria. Although extravasation staging and assessment tools exist, there is a gap in widely accepted standardized, validated, and reliable assessment tools.[56,58] Ong and Van Gerpen[58] report that there have been many iterations of extravasation staging. Extrapolating from these studies, they proposed an extravasation staging rating on a 1-4 scale that includes capillary refill time, skin temperature, percentage of swelling, blanching, and the presence of pulse below the extravasation. Regardless of the scale used, a standardized, policy-supported approach to extravasation assessment, follow-up, and documentation is recommended.

CONCLUSION

This guideline is informed by a systematic review of evidence on antineoplastic extravasation management and associated patient outcomes developed by an interprofessional panel including a patient representative. For consistency in interpretation of the recommendations, the guideline includes a table explaining strong versus conditional recommendations as they apply to patients, clinicians, researchers, and policymakers. In addition to the recommendation summary, each PICO question addressed within the guideline provides

the certainty of evidence level. The combination of the recommendation and certainty of evidence can be used to inform evidence-based processes related to antineoplastic extravasation in various practice settings.

A challenge in reviewing this body of evidence is the multiple cointerventions used to manage an extravasation, limiting the certainty of any single intervention effect over another. The potential for significant morbidity when extravasation occurs influenced the strong recommendation for pharmacologic antidote use, despite the low certainty of evidence. The adverse event profiles of four antidotes were considered in relation to potential benefit of administration, and ultimately, antidote was recommended over no antidote or conservative management alone. Paclitaxel and docetaxel were considered separately. For these agents, the panel issued a conditional recommendation for the use of an antidote. In the evidence reviewed, hyaluronidase was the antidote used. Despite low certainty of evidence, the panel noted that the potential harm from hyaluronidase use was trivial compared with potential benefits on extravasation of paclitaxel or docetaxel. The use of a thermal compress compared with no compress and applied several times per day for several days, rather than for 24 hours or less, was conditionally recommended based on very low certainty of evidence and no reports of compress-related adverse events. Finally, surgical referral or escalation to specialty care for central line extravasation management was conditionally recommended over conservative management alone. The panel focused on central lines because of the lack of evidence and concerns about resource constraints when considering all peripheral extravasations. Clinical findings, severity of the extravasation, and agent inform clinical judgment on surgical or specialty care referral in these cases.

During guideline development, the panel noted several gaps in knowledge. First, general research recommendations, including cost-effectiveness studies for all interventions, are needed to understand the impact on patients and systems, including the cost of time, supplies, prevention of secondary infection, and referrals after extravasation. Next, with the growth in antineoplastic therapy options, there is a scarcity of evidence around extravasation management for novel agents. Multiple case reports have been published on skin and tissue injury, including necrosis after extravasation of antibody–drug conjugates, especially those with microtubule disrupting agent auristatin E as the cytotoxic payload.[59–65] Publication of observational data and case reports, including management and associated patient outcomes, as well as continuous postmarketing reporting, is encouraged to develop standardized care recommendations.

Education, assessment, and treatment of extravasation are the responsibility of the interprofessional team including nurses, advanced practice providers, oncologists, pharmacists, and other specialists. Reporting on outcomes of implementing guideline-concordant care in the oncology setting serves to strengthen the evidence base for future recommendations.

RELATED ASCO GUIDELINES

- Palliative Care for Patients With Cancer[68] (https://ascopubs.org/doi/10.1200/JCO.24.00542)
- Patient-Clinician Communication[69] (https://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy[70] (https://ascopubs.org/doi/10.1200/JCO.23.00933)

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, clinical tools and resources, visit https://www.asco.org/supportive-care-guidelines. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at https://www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at http://www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at http://www.asco.org/guidelines.

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DISCLAIMER

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Oncology Nursing Society.

EDITOR'S NOTE

This Oncology Nursing Society (ONS) and American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including supplements, clinical tools, and resources, and links to patient information at http://www.cancer.org, is available at https://www.asco.org/supportive-care-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

ONS/ASCO Guideline on the Management of Antineoplastic Extravasation

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Management of Antineoplastic Extravasation: ONS-ASCO Guideline, Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Tanya Thomas, DNP, APRN, AGCNS-BC, OCN	University of Virginia Health, Charlottesville, VA	Clinical Nurse Specialist
Caroline Clark, MSN, APRN, AG-CNS-BC, OCN®, EBP-C	Oncology Nursing Society, Pittsburgh, PA	Evidence-based Practice, Guidelines, and Quality
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Kerri Dalton DNP, RN, AOCNS®	Duke Cancer Institute, Durham, NC	Clinical Nurse Specialist
Celestine G. Gochett, PhD, AOCNS®, ACNS-BC	Northside Hospital, Atlanta, GA	Clinical Nurse Specialist/Nurse Scientist
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Gwen King, RN, BSN, OCN®	University of Colorado, Aurora, CO	Oncology Infusion Nurse
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Holly Anderson, RN, BSN	Rochester, NY	Patient Representative
Kerri A. Moriarty, MLS	Oncology Nursing Society, Pittsburgh, PA	Research Specialist
Karen DiValerio Gibbs, PhD, MSN/MPH, RN, CPN	University of Texas Health Science Center at Houston, Houston, TX; Evidence Foundation, Cleveland, OH	Guideline and Evidence Synthesis Methodology
Rebecca L. Morgan, PhD, MPH	School of Medicine, Case Western Reserve University, Cleveland, OH; Evidence Foundation, Cleveland, OH; Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada	Guideline and Evidence Synthesis Methodology
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