Hyaluronidase for Treatment of Intravenous Extravasations

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SCHEME FOR GRADING THE STRENGTH AND CONSISTENCY OF EVIDENCE IN THE GUIDELINE

Standardized methods developed by The University of Iowa Nursing Intervention Research Center Research Translation and Dissemination Core Guidelines for Developing Guidelines (Titler & Adams, 2005) were followed to conduct a systematic review and synthesize current evidence on hyaluronidase for the treatment of intravenous extravasations. Research findings and other evidence, such as guidelines and standards from professional organizations, case reports and expert opinion were critiqued, analyzed and used as supporting evidence. The practice recommendations were assigned an evidence grade based upon the type and strength of evidence from research and other literature.

The grading schema used to make recommendations in this evidence-based practice guideline is:

A1 = Evidence from well-designed meta-analysis, well-done systematic review, or regulating body review with results that consistently support a specific action (e.g., assessment, intervention, or treatment)

A2 = Evidence from one or more randomized controlled trials with consistent results

B1 = Evidence from high-quality evidence-based practice guideline

B2 = Evidence from one or more evidence-based guideline or research and clinical review with consistent results

C1 = Evidence from observational studies with consistent results (e.g., correlational, descriptive studies)

C2 = Inconsistent evidence from observational studies or controlled trials

D = Evidence from expert opinion, multiple case reports, or national consensus reports

The University of Iowa College of Nursing Research Translation and Dissemination Core Scheme for Grading the Strength and Consistency of Evidence in the Guideline were adapted for this guideline in the following ways:

1) Systematic reviews done by government regulating bodies were considered equivalent to other well done systematic reviews and included as sources of evidence under A1.

2) Many of the evidence-based guidelines and reviews of research and clinical evidence did not report a systematic process and/or evaluation of the strength and consistency of evidence and therefore were not judged as scientifically rigorous according to the criteria for appraisal. However, the work reported was significant and where consistent results were reported, considered to be slightly less in strength than high-quality evidence-based practice guidelines. These guidelines and reports are presented as evidence under B2.

3) No quasi experimental studies were identified and were therefore omitted from the scheme allowing for the above evidence level B2.

4) Sources are listed and level of evidence is cited according to the general grade (A, B, C or D) and not differentiated by sub-class (1 and 2). It should be noted that in the absence of RCT in human subjects, a combination of levels of evidence may be strongest.
DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Databases
The primary search was conducted in January 2009 to identify all primary research reports related to hyaluronidase for the treatment of IV extravasations. Searches were performed using PubMed, CINAHL and Cochrane libraries databases to identify research reports and evidence-based practice guidelines, case studies, standards, national guidelines and governing body reports. In addition, an internet search was conducted using the Google® search engine. Secondary searches were conducted in September 2009 and October 2011 to identify new publications.

Keywords
The following keywords were used in the primary search: hyaluronidase, hyaluronidase limited to research studies, hyaluronidase limited to clinical trials, meta-analyses, randomized clinical trials. In the secondary search, the keywords were: hyaluronidase and extravasation, limited to English. The internet was used to search for evidence from the European Oncology Nursing Society, Infusion Nurses Society, Oncology Nursing Society, Micromedex® and the United States Food and Drug Administration (USFDA) websites.

Number of Documents Identified
A total of 95 from over 10,000 documents (identified by the keyword hyaluronidase) were identified for review by combining key terms and applying limits as described, searching titles, and reading abstracts. Related references were identified through PubMed and hand searching the reference list from key articles.

Inclusion and Exclusion Criteria
Inclusion criteria for the evidence to be included were: IV extravasation injuries treated with hyaluronidase. Evidence not in English was excluded. Inclusion and exclusion criteria were first screened using search strategies and then by review of each document.

Number of Documents Used
This guideline was developed using 72 documents: 27 research articles, 34 guidelines, reviews and other publications meeting the inclusion and exclusion criteria, plus 11 supplemental publications providing background were included in this guideline. Three documents met the inclusion and exclusion criteria but did not contribute to the evidence, and therefore were not included in this guideline.

Description of Method of Guideline Validation
This guideline was reviewed by experts knowledgeable of research on hyaluronidase for IV extravasations and development of guidelines. The reviewers suggested additional evidence for selected actions, inclusion of some additional practice recommendations, and changes in the guideline presentation to enhance its clinical utility. In addition, the guideline was reviewed by a member of the community with experience both as a patient and parent of hospitalized children.
INTRODUCTION

Intravenous (IV) fluid extravasations are a significant problem, particularly in pediatric populations. Extravasations are often times undiagnosed, untreated and under-reported. There is no centralized reporting system. The incidence therefore ranges, with reports of 0.1% to 6.5% in the general population (Camp-Sorrell, 1998; Schulmeister, 2007), 11% to 28% in children (Brown, Hoelzer, & Piercy, 1979; Garland et al., 1992), and 22% to 63% in high-risk populations such as newborns and adults receiving chemotherapy (Clifton-Koeppel, 2006; Goolsby & Lombardo, 2006). Vesicant extravasations are less common, between 0.01% and 6.5%, but are more likely to result in poor outcomes (Schulmeister, 2010). In 2009, the Centers for Medicare and Medicaid Services established new International Classification of Diseases (ICD-9) codes related to extravasations, which if used appropriately, may improve tracking.

Five mechanisms may activate tissue necrosis when an extravasation occurs: (a) direct cellular toxicity, (b) osmotic disturbances across the cell membrane leading to cell death, (c) ischemic necrosis, (d) mechanical compression, and (e) bacterial colonization (Khan & Holmes, 2002). Consequences of extravasation range from a short-term inflammatory response to severe necrosis requiring surgical intervention and may cause long-term disabilities. The extent of damage caused by vesicant extravasation depends on the agent administered, amount extravasated, anatomical location, and the treatment administered.

Hyaluronidase is an enzyme which acts as a spreading agent that can be used to treat IV extravasations. According to product specific information for package inserts (available on the U.S. Food and Drug Administration, Center for Drug Evaluation and Research website) (USFDA, 2009) hyaluronidase temporarily breaks down hyaluronic acid, which is a major component of the normal intercellular barrier of connective tissue; this allows for dispersion and absorption of the offending agent over a larger surface area. Within 24 to 48 hours after hyaluronidase use, the connective tissue barrier is regenerated. Hyaluronidase was first described as a spreading factor in 1928, and it has been used in a variety of ways since (Britton & Habif, 1953). In the 1950’s use in children for hypodermoclysis in dehydrated infants and local anesthesia was first reported (Bertelli, 1995). The use of hyaluronidase to treat IV infiltrations was common in the 1980’s up until the sole manufacturer (Wyeth-Ayerst) discontinued the product (Wydase®) in 2001 because of manufacturing issues (Oncology Nursing Society, 2003). In 2004, two new hyaluronidase products (Vitrase®, Amphadase®) were approved for use by the FDA (Shah, 2004; USFDA, 2009). Its re-emergence into the market has again made hyaluronidase available as an option for the treatment of extravasations.

Standardized treatment for the management of IV extravasations is lacking (Pettit & Hughes, 1999; Schulmeister, 2007; Warren, 2011; Wilkins & Emmerson, 2004). In a survey of Neonatal Intensive Care Units (NICU), less than two thirds (63%) of units had a procedure for IV extravasations and fewer (57%) had a procedure for the use of hyaluronidase (Pettit & Hughes, 1999). Because no randomized trials on the management of drug extravasation in humans has ever been completed, recommendations must be based on consistent experimental studies in animals, evidence-based guidelines and reviews, descriptive studies, cumulative clinical experience and case reports. Other sources such as regulating body reviews (USFDA) and
standards developed by special interests groups (Infusion Nurses Society, Oncology Nursing Society, European Oncology Society, Children’s Oncology Group) should also be considered.

Safety

Hyaluronidase for injection has been marketed and given safely for over 50 years (Evidence Grade = A: USFDA, 2009). Safety is supported by USFDA approval. When it was withdrawn from the market, the USFDA Drug Efficacy Study Group determined hyaluronidase was not withdrawn from sale for reasons of safety or effectiveness, leaving it open to manufacturers to develop new products (Evidence Grade = A: U. S. Department of Health and Human Services, Food and Drug Administration, November 6, 2003). The most serious adverse effects have been hypersensitivity reactions (<0.1%) that vary in severity (Evidence Grade = A: USFDA, 2009).

Studies and evidence-based reports support the safety and include neonatal (Evidence Grade = B: Banta, 1992; Sawatzky-Dickson & Bodnaryk, 2006; Thigpen, 2007), pediatric (Evidence Grade = B: Montgomery et al., 1999), and other populations of adults (Evidence Grade = B: Albanell & Baselga, 2000; Bertelli, 1995; MacCara, 1983). One hyaluronidase product, (Amphadase®) contains thimerisol, a mercury derivative, that may be concerning in developing neonatal populations (Evidence Grade = B: Thigpen, 2007) but this is not included in USFDA contraindications. No differences in safety between geriatric and younger adult patients have been noted (Evidence Grade = A: USFDA, 2009). No known differences in dose response were attributed to special population disparities including age, gender, racial or ethnic factors (USFDA, 2009).

Efficacy

The efficacy of hyaluronidase to increase absorption and dispersion of other drugs products is supported by the USFDA subcommittee evaluation (USFDA, 2009). Efficacy for treating IV extravasations is supported by randomized clinical trials in animal models (Evidence Grade = A: Disa, Chang, Mucci, & Goldberg, 1998; Dorr, Snead, & Liddil, 1996; Elam, Dorr, Lagel, & Pond, 1991; Kesik et al., 2010; Laurie, Wilson, Kernahan, Bauer, & Vistnes, 1984; Raszka, Kueser, Smith, & Bass, 1990; Zimmet, 1993, 1996), retrospective and descriptive studies in humans (Evidence Grade = C: Bertelli et al., 1994; Cochran, Bomyea, & Kahn, 2002; Federle, Chang, Confer, & Ozgun, 1998; Khan & Holmes, 2002), and clinical reports (Evidence Grade = D: Bertelli et al., 1997; Cicchetti, Jemec, & Gault, 2000; Davies, Gault, & Buchdahl, 1994; Kumar & Sprung, 2003; Martin, Carver, & Petros, 1994; North Trent Cancer Network, 2011; Sokol, Dahlmann, & Dunn, 1998; Zenk, Dungy, & Greene, 1981). Efficacy of treatment depends on the extravasated drug properties and volume (see indications), characteristics of the patient (see risk factors), timeliness of administration, dose administered and adjuvant therapies (see description of practice). While hyaluronidase efficacy is supported, there is no consensus regarding specific extravasation treatment resulting in regional and unit-based protocols that vary greatly (Evidence Grade = B: Clifton-Koeppel, 2006). Ambivalence is evident in current guidelines, for example the European Oncology Nursing Society (2007) which describes use and administration of hyaluronidase with vinca alkaloids, taxanes and other non-chemotherapy drugs, but states, while these drugs are suggested in many literature sources, further study is recommended due to a lack of evidence.
Products Available

Five hyaluronidase products have been approved by the USFDA: Amphadase®, Hydase® (discontinued 4/09), Hylenex® Recombinant (rHuPH20), Vitrase® and Wydase® (discontinued 1/01). Refer to the package insert for product specific information. See Appendix D1 for a table available products and general information. Product selection is based on availability in the institution and provider preference.

PURPOSE

The purpose of this evidence-based guideline is to aide practitioners and healthcare institutions in making evidence-based decisions regarding the use of hyaluronidase for IV extravasations in their setting. It is intended for use by nurses and licensed independent providers in health care settings where IV extravasations occur. It should be used as a reference for developing institutional policies and practices for IV extravasation care. This guideline describes the evidence-base for hyaluronidase use with IV extravasations of various agents. Preventative measures and other primary methods for treatment (including antidotes) are beyond the scope of this guideline.

The goal of managing IV extravasations is to prevent progression to tissue necrosis and ulceration. Patients with IV extravasations are expected to benefit from hyaluronidase when prompt evidenced-based treatment is indicated. Benefits to the patient include mitigation of injury, pain, disfigurement, and loss of function. Healthcare providers and institutions will benefit from these guidelines by administering hyaluronidase according to the best evidence, decreasing adverse patient outcomes, and potentially avoiding litigation.

DEFINITION OF KEY TERMS

- Antidote - Agents that neutralize a poison or counteract its effects. Note: Hyaluronidase is NOT an antidote it is better described as an enzymatic spreading factor.
- Anthracyclines - Class of chemotherapy agents that includes: doxorubicin, daunorubicin, epirubicin, idarubicin.
- Compartment Syndrome - Increased pressure within a limited anatomical space which compromises the circulation and function of tissues within the space.
- Cytotoxic - Drugs that kill cells.
- Eschar - A hard crust or scab from a burn
- Extravasation - The inadvertent administration of a vesicant or any agent into the surrounding tissue resulting in injury.
- Infiltration - The inadvertent administration of a nonvesicant agent into surrounding tissue. For the purposes of this guideline, infiltrations will also be referred to as extravasations.
- Intravenous (IV) - Into the vein.
- Intradermal (ID) - Into the dermal layer of skin.
- Irritant - Agent that causes pain at the injection site, with or without an inflammatory reaction, but without tissue necrosis.
- Neonatal - Newborns under the gestational age of 1 month or cared for by the neonatal service.
• Pediatric - Children under the age of 18 years or cared for by the pediatric service.
• Radiation re-call - A severe skin reaction that occurs when certain chemotherapy drugs are administered during or soon after radiation treatment.
• Re-call - A severe skin reaction that is a side effect induced by one chemotherapy agent and later occurs when the patient is given a different chemotherapy regimen.
• Vinca alkaloids - Class of chemotherapy agents that includes: vinblastine, vincristine, vindesine and vinorelbine
• Vesicant - Medication or solution that has the potential to cause blistering or ulceration when inadvertently administered into the tissue.

**ASSUMPTIONS**

**Prevention of Extravasation Injuries is the Best Treatment and Should Be the Goal**

Established guidelines for safely administering standard IV therapy and vesicant drugs should be followed to prevent IV extravasations from occurring (Evidence Grade = B: Albanell & Baselga, 2000; Goolsby & Lombardo, 2006; MacCara, 1983; Schulmeister, 2010. Evidence Grade = D: Doellman et al., 2009; Infusion Nurses Society, 2011; North Trent Cancer Network, 2011).

An extravasation prevention plan that defines the skill competencies for nurses should be considered (Evidence Grade = B: Dorr, 1990; MacCara, 1983. Evidence Grade = D: Infusion Nurses Society, 2011). Each nurse who administers intravenous medications should be educated and clinically competent. Specific education for the administration of chemotherapeutic agents is described in oncology nursing standards and guidelines (Evidence Grade = A: COG Pharmacy Committee & COG Nursing Clinical Practice Committee: Acute/Palliative Care Section, 2007). However, extravasation injuries may occur even in the most closely monitored situations (Evidence Grade = D: Stanley, 2007).

**Evidence-Based Guidelines for Interventions and Treatment of Extravasations should be established in Organizational Policies and Procedures** (Evidence Grade = B: Camp-Sorrell, 1998; European Oncology Nursing Society, 2007; Goolsby & Lombardo, 2006; Montgomery et al., 1999; Schulmeister, 2011. Evidence Grade = D: Infusion Nurses Society, 2011; Jacobson et al., 2009).

Grouping or bundling IV interventions and treatments together under one standard of care is an effective implementation strategy. See Appendix E1 for an example of an institutional evidence-based standard of care.

**INDIVIDUALS/PATIENTS AT RISK FOR IV EXTRAVASATIONS**

**Neonatal, Pediatric and Elderly Patients**

Most extravasation injuries occur in infants who are 26 weeks gestation and less. Preterm infant are at greatest risk because of immature skin, difficult access and longer durations for IV therapy. NICU patients are at increased risk for extravasation because of small blood vessels with low blood flow which allows for less hemodilution of agents during infusions. Preterm infants have less subcutaneous fat at IV sites such as the hands, feet, and scalp. As a result, even
isotonic solutions such as 5% dextrose can result in necrosis and blistering in this population (Evidence Grade = B: Clifton-Koeppel, 2006; MacCara, 1983).

Patients at highest risk for extravasation include very young children and the elderly (Evidence Grade = B: MacCara, 1983). The risk of compartment syndrome is greatest in infants and young children (Evidence Grade = B: Clifton-Koeppel, 2006). Elderly patients may have fragile skin and veins, general debility, and reduced pain sensation (Evidence Grade = D: Stanley, 2007).

**Patient Conditions**

Patients receiving cancer therapies have multiple risk factors (e.g. poor access, chemotherapy, radiation) making IV infusion difficult and are at higher risk for extravasation than the general population (Evidence Grade = B: European Oncology Nursing Society, 2007).

Patients with small fragile, mobile, or hard sclerosed veins, limited IV sites, long-term IV therapy and multiple sticks or probing during IV insertion are at increased risk for extravasation because of poor IV access (Evidence Grade = B: Camp-Sorrell, 1998; European Oncology Nursing Society, 2007; Goolsby & Lombardo, 2006; Schulmeister, 2011).

Patients with uncontrolled movements including seizures, coughing, retching, or hyperactivity can cause the IV to move and therefore making them at risk for extravasation (Evidence Grade = B: Camp-Sorrell, 1998).

Patients who are sedated or unable to communicate are at increased risk for extravasation because they are unable to report pain (Evidence Grade = B: Camp-Sorrell, 1998; European Oncology Nursing Society, 2007; Goolsby & Lombardo, 2006; Schulmeister, 2011. Evidence Grade = D: Stanley, 2007).

Patients with impaired circulation, lymphedema, mastectomy, superior vena cava syndrome or peripheral neuropathies are at increased risk for extravasation because of edema and altered pain sensation (Evidence Grade = B: Camp-Sorrell, 1998; European Oncology Nursing Society, 2007; Goolsby & Lombardo, 2006; MacCara, 1983; Schulmeister, 2011).

Patients with recall phenomenon, previous local irradiation (radiation re-call) or scarring causing damage to the veins are at increased risk for extravasation (Evidence Grade = B: Goolsby & Lombardo, 2006; MacCara, 1983. Evidence Grade = D: Stanley, 2007).

Patients with co-morbidities (e.g., diabetes, circulatory disorders, obesity) are at increased risk for extravasations (Evidence Grade B: European Oncology Nursing Society, 2007; Schulmeister, 2011).

**Practitioner Knowledge and Skill**

Practitioners need specific and specialized knowledge and skills for IV therapy and vesicant administration. Lack of knowledge or skill by the practitioner puts the patient at increased risk for extravasation (Evidence Grade = B: Camp-Sorrell, 1998; European Oncology Nursing
Hyaluronidase for Treatment of Intravenous Extravasations

Evidence-Based Guideline

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Mechanical Injectors/Rate of Administration

Mechanical factors contributing to risk for extravasation may include: small size and poor condition of the veins, large catheter size relative to the vein size, site choice, unstable catheter, poor securement of a port access needle, patient activity, multiple sites on the same extremity, use of a pump of power injector, catheter port separation or line fracture (Evidence Grade = B: Schulmeister, 2011. Evidence Grade = D: Doellman et al., 2009).

Extravasation of contrast material is more prevalent with use of mechanical injectors (Evidence Grade = C: Cochran, Bomyea, & Kahn, 2002; Federle et al., 1998; MacCara, 1983). Power injectors allow rapid infusion of contrast materials, but may not be able to detect when an extravasation occurs. By the time pressure exceeds set limits, it is likely that the extravasation volume is large (Evidence Grade = B: Earhart & McMahon, 2011).

Extravasation of contrast material may or may not be more prevalent with increased rate of administration (Evidence Grade = C: Cochran et al., 2002; Federle et al., 1998).

High-Risk Agents

The potential of each agent to cause tissue necrosis when extravasated is not uniform. Chemotherapy agents classified as vesicants have the highest risk of causing injury when extravasated. There are two sub-categories of vesicant chemotherapy: DNA binding and non-binding agents. DNA binding agents (e.g., anthracyclines) bind to the DNA in cells and when the cells die are released into the tissue and re-circulated, resulting in tissue damage over a longer period of time and larger, deeper, more painful injuries (Evidence Grade = B: Schulmeister, 2007, 2011. Evidence Grade = D: Doellman et al., 2009). DNA non-binding agents (e.g., vinca alkaloids) do not bind DNA and have an indirect effect on tissue resulting in localized injuries that improve with time. Irritant medications are also capable of causing local toxicity.

Nonvesicant drugs are at lower risk for causing extravasations, but even with these agents, damage sometime occurs (Evidence Grade = B: Albanell & Baselga, 2000; Bertelli, 1995; European Oncology Nursing Society, 2007. Evidence Grade = D: Doellman et al., 2009). See Appendix A1 for a table of chemotherapy medications at high risk for causing injury with IV extravasation.

There are many other (non-chemotherapy) agents that cause damage when extravasated. Hyperosmotic agents have higher than serum osmolarity (281-289 mOsm/L), causing fluid shift and cell damage due to osmotic factors. Catecholamines and vasopressors are high risk agents because they induce ischemic necrosis when extravasated. Other agents that are high risk are those that are very alkaline, poorly water soluble, or other irritants (Evidence Grade = B: MacCara, 1983; Montgomery et al., 1999; Thigpen, 2007. Evidence Grade = D: Doellman et al., 2009). See Appendix A2 for a table of (non-chemotherapy) agents at high risk for causing injury with IV extravasation.
IV Location

Extravasations in areas of flexion (e.g., the wrist, foot or elbow) or where there is minimal underlying tissue (e.g., the wrist and dorsum of the hand or foot) tend to be more severe than injuries in other areas (e.g., the forearm) (Evidence Grade = B: Schulmeister, 2007, 2011. Evidence Grade = D: Stanley, 2007).

ASSESSMENT CRITERIA

The following assessment criteria indicate patients who are likely to benefit the most from use of this evidence-based guideline:

Ongoing Observation and Assessment

It is difficult to determine the extent of extravasation injury from the early appearance of the site. The initial symptoms may occur immediately however, progression varies greatly depending on the agent (e.g., for a DNA binding vesicant versus an irritant) and tissue damage (Evidence Grade = B: European Oncology Nursing Society, 2007. Evidence Grade = D: Doellman et al., 2009). Therefore, ongoing assessment and early treatment are indicated (Evidence Grade = B: Bertelli, 1995; Camp-Sorrell, 1998; Clifton-Koeppel, 2006).

The patient is often the first person to be aware that something is wrong with their IV. They should be instructed to report any changes during treatment (Evidence Grade = D: North Trent Cancer Network, 2011; Stanley, 2007). Particularly with vesicant drugs, patients should be aware of the risks associated with administration and instructed to call the nurse immediately if there is any pain or discomfort at the infusion site (Evidence Grade = A: COG, 2007. Evidence Grade D: Infusion Nurses Society, 2011).

Evidence of extravasation may include*:

- Loss of blood return (may be misleading sign whether present or absent)
- Leakage at the site
- Slow infusion or resistance to infusion, change in infusion flow, occlusion alarms
- Pain or burning at the site (persistent pain indicates more severe injury)
- Coolness of skin
- Erythema
- Edema
- Blistering (indicates at least partial thickness skin injury)
- Mottling
- Blanching
- Darkening of the skin
- Inflammation (occurs later)
- Induration (if occurs early may indicate eventual ulceration, generally occurs later)
- Sloughing (occurs later)
- Dry, black eschar (occurs later)
• Ulceration with typical necrotic, yellowish fibrotic base and surrounding rim of persistent erythema (occurs later)
  *Not all these symptoms may be present (Evidence Grade = B: European Oncology Nursing Society, 2007; Goolsby & Lombardo, 2006; Thigpen, 2007. Evidence Grade C: Pettit & Hughes, 1999. Evidence Grade = D: North Trent Cancer Network, 2011, Stanley, 2007)

**Evidence of extravasation with a central venous access device** may also include:
• Aching or discomfort in the shoulder, neck, or chest wall
• Pain or burning of chest wall
• Leakage at the exit site or along subcutaneous canal
• Swelling of the chest wall
(Evidence Grade = D: North Trent Cancer Network, 2011)

**Evidence of compartment syndrome** may include:
• Tense edema
• Pain
• Reduced capillary refill (>4 seconds)
• Skin breakdown
(Evidence Grade = B: Clifton-Koeppel, 2006)

**Evidence of other IV complications** distinguishing between extravasations and other local reactions is an important step in diagnosis. Other conditions that resemble extravasations include:
• Flare reaction
• Vessel irritation
• Venous shock
• Phlebitis
• Hypersensitivity

The principle difference between these conditions and an extravasation relates to the agent administered and the nature and timing of symptoms including pain, erythema, and swelling (Evidence Grade = B: European Oncology Nursing Society, 2007). See Appendix A3 for symptoms distinguishing an IV extravasation from other conditions.

**IV Staging Tool**

A standardized scale should be used to assess and document the grade of the extravasation (Evidence Grade = B: Clifton-Koeppel, 2006; Flemmer & Chan, 1993. Evidence Grade = D: Infusion Nurses Society, 2011). The Infusion Nurses Society (INS) infiltration scale is easy to use, valid, and reliable (Groll, Davies, Mac Donald, Nelson, & Virani, 2010).

When using a standard scale to document extravasations in neonates and pediatric patients, measurements appropriate to the child’s size should be considered. The grade should be determined according to the presence of the most severe indicator. Vesicant extravasations should always be rated a grade 4 due to the potential for such injuries (Evidence Grade = D: Infusion Nurses Society, 2006).
Stage 1-2 extravasations require conservative treatment including documentation, elevation, and thermal modalities. Most will resolve spontaneously after the IV is removed but treatment with hyaluronidase may be considered if indicated (Evidence Grade = B: Flemmer & Chan, 1993; Thigpen, 2007).

Stage 3-4 extravasations require prompt and aggressive intervention including treatment with hyaluronidase if indicated (Evidence Grade = B: Flemmer & Chan, 1993; Thigpen, 2007).

See Appendix A4 for INS staging tool.

**Clinical Algorithms**

Clinical algorithms guide practitioners through assessments, timely decision making processes, and standardize care (Evidence Grade = B: European Oncology Nursing Society, 2007; Montgomery et al., 1999; Wickham, Engelking, Sauerland, & Corbi, 2006).

See Appendix A5 for examples of clinical algorithms.

**Identify Indications for Treatment**

Hyaluronidase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs (Evidence Grade = A: USFDA, 2009).

See Appendix D2 for a table of evidence supporting the efficacy of hyaluronidase with specific agents for medication specific indications. Not every agent is included; consultation with pharmacy and licensed independent provider for agents not included is advised.

**Identify Contraindications for Treatment**

Hypersensitivity to hyaluronidase or any of the ingredients in the formulation is a contraindication to use. Discontinue use if hypersensitivities occur (Evidence Grade = A: USFDA, 2009).

Hyaluronidase should NOT be used with dopamine or alpha agonist drugs (Evidence Grade = A: USFDA, 2009).

Hyaluronidase should NOT be injected into tumors, acute inflamed or infected areas because of the danger of spreading the infection to other tissues (Evidence Grade = A: COG, 2007; USFDA, 2009. Evidence Grade = B: Dorr, 1990).

Hyaluronidase should NOT be used for IV injection because the enzyme is rapidly inactivated (Evidence Grade = A: USFDA, 2009).

Use with anthracyclines extravasations should be considered with extreme caution due to mixed reports; other treatments are recommended (Evidence Grade = B: Dorr, 1990).
Recombinant human hyaluronidase contains no animal derivatives, limiting the risk of allergic responses (Evidence Grade = D: Kuensting, 2010).

**Documentation**

The purpose of documentation is to provide a clear record of what happened and the action taken. In addition to routine documentation of IV insertions and maintenance, careful documentation of every extravasation incident should be documented in the patient’s medical record. Proper documentation should include: signs and symptoms of extravasation, interventions implemented and patient response to treatment (Evidence Grade = D: Infusion Nurses Society, 2011), more specifically, it may include:

- Date and time of extravasation
- IV site location, patency, and appearance (color, edema, blistering, etc.), including measures of the area of injury
- Catheter type and size
- Name of the extravasated agent, dose, route, and dilution
- Administration technique (e.g., bolus, infusion)
- Description of blood return before and during vesicant administration
- Estimated amount of the extravasation
- Amount of drug aspirated
- Assessment of the extremity; range of motion, discomfort
- Digital photographic documentation of the site, marked with the date and time, is advised after the initial injury and at regular intervals as needed to follow progression of the injury
- Mark the area of injury with indelible pen
- Interventions and treatments, date and time
- Patient symptoms and comments
- Notification of the licensed independent provider and any consulting services
- Patient and caregiver education (see below)
- Follow up instructions

Documentation of extravasations may be within the institutional system, on separate incident forms or both. See Appendix A6 for examples of extravasation documentation forms.

**Patient and Caregiver Education**

Patient and caregivers should routinely be provided with education about IV assessment (e.g., skin assessment, reporting pain and other symptoms).

Patient and caregivers should be provided with education when an extravasation occurs regarding the possible progression of signs and symptoms, changes to report, protecting the area from sunlight, and follow-up care (Evidence Grade = D: Infusion Nurses Society, 2011).
Hyaluronidase for Treatment of Intravenous Extravasations

Overdosage

After treating with hyaluronidase, assess for symptoms of hyaluronidase toxicity including:

- Local edema or urticaria
- Erythema
- Chills
- Nausea
- Vomiting
- Dizziness
- Tachycardia
- Hypotension

The enzyme should be discontinued and supportive measures initiated immediately (Evidence Grade = A: USFDA, 2009).

DESCRIPTION OF THE PRACTICE

Immediately Stop the Infusion but DO NOT Remove Cannula


Evacuate the Extravasate

Try to evacuate the offending agent through the original catheter, if it is still in place, by aspirating any residual drug using a 1-10 ml syringe (Evidence Grade = B: Albanell & Baselga, 2000; Camp-Sorrell, 1998, COG, 2007; Dorr, 1990; European Oncology Nursing Society, 2007; Flemmer & Chan, 1993; Goolsby & Lombardo, 2006. Evidence Grade C: Bertelli et al., 1994; Khan & Holmes, 2002. Evidence Grade = D: Doellman et al., 2009; North Trent Cancer Network, 2011).

Other methods for extraction, including the “squeeze maneuver” needle aspiration, liposuction, surgical fenestration and irrigation are not routinely recommended (Evidence Grade = D: Doellman et al., 2009). Avoid excess pressure at the site. Some evidence suggests pressure at the site can spread the drug to a broader area and should be avoided (Evidence Grade = B: Albanell & Baselga, 2000; Camp-Sorrell, 1998; Dorr, 1990; Wickham et al., 2006. Evidence Grade = C: Bertelli et al., 1994. Evidence Grade D: Infusion Nurses Society, 2006). Others recommend gently massage area to facilitate dispersal (Evidence Grade = D: North Trent Cancer Network, 2011; Stanley, 2007).

Determine if IV Site is Needed for Treatment
If a medication is extravasated, treatment should be determined prior to removal (Evidence Grade = B: Dorr, 1990. Evidence-Grade = D: Infusion Nurses Society, 2011; North Trent Cancer Network, 2011).

There is conflicting anecdotal evidence regarding the administration of hyaluronidase through the existing catheter (Evidence Grade = B: MacCara, 1983; Montgomery et al., 1999; Schulmeister, 2007). Some argue that administering hyaluronidase through the existing catheter may circulate the offending agent further (Evidence Grade = B: COG, 2007) or increases the risk of IV administration (Evidence Grade = A: Schulmeister, 2007; USFDA, 2009), which does not allow it to disperse the extravasated agent in the tissue. Others advocate for using a technique of pulling the catheter back 1 to 2 mm to avoid IV injection and using the existing catheter to administer hyaluronidase into the same tissue plane as the extravasated medication (Evidence Grade = B: Flemmer & Chan, 1993; Goolsby & Lombardo, 2006; Wickham et al., 2006).

**Discontinue Peripheral IV**

If the IV site is not needed for treatment, remove the catheter so that the site can no longer be used as an IV route (Evidence Grade = B: Banta, 1992; Camp-Sorrell, 1998; Schulmeister, 2007. Evidence Grade = C: Khan & Holmes, 2002). Do not use the extremity for subsequent IVs (Evidence Grade = D: Infusion Nurses Society, 2006).


**Administer Hyaluronidase As Soon As Possible After the Event**

Timely administration is a key factor in achieving positive results. Delayed treatment of > 1 hour may be less effective (Evidence Grade = B: Laurie et al., 1984. Evidence Grade = A; Banta, 1992; Clifton-Koeppel, 2006; Flemmer & Chan, 1993; Montgomery et al., 1999. Evidence Grade = D: Napoli et al., 2005).

There are no clear rules as to how long after an extravasation occurs that treatment may be beneficial (Evidence Grade = D: Stanley, 2007). One case reported administration 10 days after unrecognized vinorelbine extravasation resulted in disappearance of pain and redness at site within 24 hours (Evidence Grade = C: Bertelli et al., 1994).

Prompt administration of hyaluronidase, which should absorb extravasated drug in the tissue, would likely also have the added advantage of decreasing “recall” phenomenon with later therapy in drugs that exhibit this effect (Evidence Grade = D: Bertelli et al., 1997).

**Follow Manufactures’ Recommendations for Administration**

**Dosage**

The recommended dosage for hyaluronidase varies with different protocols from 15-1,500 units (Evidence Grade = B: European Oncology Nursing Society, 2007; Montgomery et al., 1999; Schulmeister, 2011. Evidence Grade = D: North Trent Cancer Network, 2011).
Hyaluronidase for Treatment of Intravenous Extravasations

Network, 2011), most typically for absorption and dispersion of chemotherapy drugs, 150 units hyaluronidase in 1 ml fluids is injected (Evidence Grade = A: USFDA, 2009. Evidence Grade = B: COG, 2007; European Oncology Nursing Society, 2007; Schulmeister, 2007, 2009). Protocols for neonatal and pediatric use typically recommend 15 units hyaluronidase in 1 ml saline as a recommended dose (Evidence Grade = B: Banta, 1992; Flemmer & Chan, 1993; Montgomery et al., 1999). Higher doses may be used with saline flush out (see adjuvant therapies).

**Route**
Hyaluronidase may be given subcutaneous or intradermal, IV administration should be avoided because the enzyme is rapidly deactivated (Evidence Grade = A: USFDA, 2009).

**Reconstitution**
Hyaluronidase is typically reconstituted with normal saline and often further diluted to make a solution of the desired units/ml for administration (Evidence Grade = A: USFDA, 2009). Consult with pharmacy about reconstitution of specific units/ml solutions.

**Administration**
If a peripheral IV access device is still in place, pull the catheter back 1-2 mm (to avoid IV administration) and give the whole dose through the catheter (Evidence Grade = B: Banta, 1992; Flemmer & Chan, 1993; Montgomery et al., 1999; Schulmeister, 2011).

**Alternatives**
If peripheral IV access has been discontinued or if choosing to distribute hyaluronidase over greater surface, often 0.2-0.25 ml in 4-5 tuberculin syringes (1ml total) is administered SQ or ID from the leading edge of the affected area to the center of the site with 25 gauge needles (Evidence Grade = B: Banta, 1992; COG, 2007; European Oncology Nursing Society, 2007; Flemmer & Chan, 1993; MacCara, 1983; Montgomery et al., 1999; Schulmeister, 2009; Thigpen, 2007).

Others report much higher doses and volumes (Evidence Grade = D: North Trent Cancer Network, 2011), particularly when done in conjunction with saline flush out (see adjuvant therapies to follow) or based on the volume of chemotherapy extravasations, for example 1 to 6 ml of 150 unit/ml solution or 1 ml of solution for 1 ml of extravasated drug (Evidence Grade = B: Schulmeister, 2007, 2010, 2011).

Recombinant hyaluronidase may be more pure than animal-derived sources, thereby requiring fewer injections (Evidence Grade = D: Kuensting, 2010).
Figure 1. Administration of hyaluronidase in 4 aliquots. See Appendix D6 figure for administration in 5 aliquots.

**Consider Repeating As Needed**

There are no clear rules as to how often or when hyaluronidase can be given again (Evidence Grade = B: Montgomery et al., 1999).

**Assess and Manage Pain**

Pain due to the extravasation should be managed with supportive interventions. Mild pain may require systemic analgesics and non-pharmacologic comfort measures. Moderate to severe pain may require oral or IV opioids (Evidence Grade = B: European Oncology Nursing Society, 2007; Schulmeister, 2007; Wickham et al., 2006. Evidence Grade = D: North Trent Cancer Network, 2011).

**ADJUVANT THERAPIES**

Other therapies may enhance the effectiveness of hyaluronidase.

**Positioning**

Elevation of the affected site for 24 to 72 hours to decrease edema and aid in normal absorption of extravasated fluids (Evidence Grade = B: Albanell & Baselga, 2000; Banta, 1992; Camp-Sorrell, 1998; Dorr, 1990; MacCara, 1983; Wickham et al., 2006. Evidence Grade = D: Doellman et al., 2009).

**Thermal modalities**

Dry heat is recommended for vinca alkaloids (e.g., vincristine, vinblastine, vinorelbine) extravasations (Evidence Grade = B: Albanell & Baselga, 2000; Bertelli, 1995; Camp-Sorrell, 1998; Schulmeister, 2010, 2011. Evidence Grade = D: Stanley, 2007). To disperse and dilute, warm compresses may be applied for 20 minutes four times a day for 1-2 days (Evidence Grade = B: European Oncology Nursing Society, 2007).
With the exception of vinca alkaloids, there is no clear evidence regarding the benefit of thermal modalities with hyaluronidase. In general, topical cooling appears to be a better choice after extravasations (Evidence Grade = D: Stanley, 2007). However the mechanism of cooling is opposed to hyaluronidase (i.e., localizing the extravasate), whereas warming works with hyaluronidase to increase blood flow to the area and disperses it.

Cold (but not hyaluronidase) is recommended for anthracycline (e.g., doxorubicin, daunorubicin). Heat increases the cytotoxicity of these agents and should be avoided (Evidence Grade = B: Albanell & Baselga, 2000; Bertelli, 1995; Dorr, 1990; Goolsby & Lombardo, 2006; Schulmeister, 2011). Other DNA-binding vesicant extravasations may also benefit from cooling (Evidence Grade = B: Schulmeister, 2010). The optimal cooling pattern is not known. Intermittent cooling according to patient tolerance for up to 24-72 hours is suggested but benefits are seen with less aggressive schedules (Evidence Grade = A: Elam et al., 1991. Evidence Grade = B: Bertelli, 1995; Camp-Sorrell, 1998; Dorr, 1990).

Moist heat should be avoided, particularly in neonates; it can cause tissue maceration (Evidence Grade = B: Banta, 1992; MacCara, 1983. Evidence Grade = D: Doellman et al., 2009; Infusion Nurses Society, 2011; Stanley, 2007). The use of topical heat or cold for infiltrations in neonates is discouraged (Evidence Grade = B: Association of Women’s Health, Obstetric and Neonatal Nurses, AWHONN, 2007).

**Saline Flush Out**

Saline flush out or dispersal with saline is a technique that physically removes any extravasated material from the tissue while conserving the skin (Evidence Grade = C: Khan & Holmes, 2002. Evidence Grade = D: Doellman et al., 2009). Flushing the site with saline may be indicated when multiple agents have extravasated (Evidence Grade = D: Martin et al., 1994) or for large volumes or vesicant agents (Evidence Grade = D: Dougherty & Oakley, 2011). While saline flush out alone can be effective for decreasing tissue damage, it is less effective than hyaluronidase (Evidence Grade = A: Raszka et al., 1990). Often, saline flush out is used in conjunction with hyaluronidase; however there is insufficient evidence to compare the efficacy or synergy of this additional therapy (Evidence-Grade = B: Clifton-Koeppel, 2006. Evidence Grade = C: Khan & Holmes, 2002; Schulmeister, 2011. Evidence Grade = D: Bertelli, Garrone, Bighin & Dini, 2001; Cicchetti et al., 2000; Davies, Gault, & Buchdahl, 1994; Dougherty & Oakley, 2011).

Techniques for saline washout vary from multiple injections or stab wounds, with or without irrigation and manual squeezing, to surgical incisions, fluorescence microscopy, irrigation, and liposuction. Local or general anesthesia may be required (Evidence Grade = B: Clifton-Koeppel, 2006; Schulmeister, 2007; Wickham et al., 2006. Evidence Grade = D: Davies et al., 1994; Doellman et al., 2009; Dougherty & Oakley, 2011; Napoli et al., 2005).

**Dressings and Topicals**

Promotion of a moist wound environment using various topicals and dressings reduces healing time, decreases incidence of infection and prevents undue scarring (Evidence Grade = B: Clifton-Koeppel, 2006; Thigpen, 2007).
Occlusive dressings such as hydrocolloid dressings and hydrogel sheets and amorphous gel has been recommended for infiltration wounds in neonates (Evidence Grade = B: AWHONN, 2007; Sawatzky-Dickson, & Bodnaryk, 2006). Others warn that dressings and topical medications should be used with extreme caution in neonates because of concern for percutaneous absorption of toxins in this population (Evidence Grade = B: Clifton-Koeppel, 2006). Silver sulfadiazine 1% (Silvadene®) is not recommended for infants < 30 days old due to concerns for kernicterus (Evidence Grade = B: Montgomery et al., 1999) and topical 2% nitroglycerin should be avoided in term infants less than 21 days old (Evidence Grade = B: AWHONN, 2007).

See Appendix D for tables of dressings and topicals.

Surgical Consultation and Intervention

It is important to remove any residual cytotoxic drug however, the need for early surgical versus conservative treatment is controversial (Evidence Grade = B: Bertelli, 1995; Schulmeister, 2007; Wickham et al., 2006. Evidence Grade = C: Khan & Holmes, 2002). Surgical treatment is indicated for large volume extravasations, compartment syndrome, deep extravasation through a central line, severe pain up to 2 weeks after the injury or if treatment with hyaluronidase fails to prevent progression of the injury. Surgical treatment for anthracyclines and other DNA-binding agents may be indicated to prevent damage over time. Surgical treatment may consist of saline flush out, debridement, excision of infiltrated tissue, grafting, complex reconstruction or amputations (Evidence Grade = B: Bertelli, 1995; Camp-Sorrell, 1998; Dorr, 1990; Goolsby & Lombardo, 2006; Langer, Sehested, & Jensen, 2009; Schulmeister, 2007, 2011; Wickham et al., 2006. Evidence Grade = D: Stanley, 2007).

Fluorescence Microscopy

Intraoperative fluorescence injections are used to demarcate viable tissue and locate deposits of medications such as anthracyclines and guide surgical excision of necrotic tissues (Evidence Grade = B: Dorr, 1990; Langer et al., 2009; Schulmeister, 2007; Wickham et al., 2006).

STRATEGIES AND TOOLS FOR IMPLEMENTING

Computerized or Standing Order Sets

Antidote order sets should be readily accessible (Evidence Grade = D: Jacobson et al., 2009).

Computerized Documentation Systems

Computerized documentation systems that force nurses to chart against specific assessment criteria increases the compliance with outcome indicators (Evidence Grade = B: Montgomery et al., 1999).

Administration Kits
It is highly recommended that healthcare professionals administering IV therapy have the supplies and instructions for managing IV extravasations from a variety of agents in a quickly accessible kit. The kit should be checked regularly and restocked following use (Evidence Grade = B: European Oncology Nursing Society, 2007; Thigpen, 2007. Evidence Grade = C: Khan & Holmes, 2002. Evidence Grade = D: Jacobson et al., 2009). Kits may include:

- Indelible pen for marking affected area
- Alcohol swabs
- 3 ml and 10 ml syringes (for aspirating extravasate)
- Gauze squares
- Cold and warm compresses
- Institutional policy and procedures
- Management algorithm
- 25-30 gauge needles
- Instructions for reconstitution of hyaluronidase
- 5 appropriate syringes for administering hyaluronidase
- Hyaluronidase and saline
  (Evidence Grade = B: European Oncology Nursing Society, 2007; Wickham et al., 2006)

Rapid Response Mechanism

It is important to get expertise to the bedside rapidly (Evidence Grade = D: Stanley, 2007). Extravasation injuries should be seen as an emergency and treated immediately (within hours) in order to limit damage and prevent severe and disfiguring ulcerations (Evidence Grade = D: Napoli et al., 2005).

Clinical Algorithms

Population and institution specific evidence-based clinical algorithms guide practitioners through timely decision making processes and standardize care (Evidence Grade = B: European Oncology Nursing Society, 2007; Montgomery et al., 1999; Wickham et al., 2006). See Appendix A5 for examples of algorithms.

Quick Reference Cards

To assist with compliance with institutional protocols, staff can be given pocket quick reference cards instructing them what to do when there is an extravasation (Evidence Grade = B: Montgomery et al., 1999). See Appendix D for examples of quick reference cards.

Nursing Intervention Classification

The Nursing Interventions Classification (NIC) is a comprehensive, standardized classification of interventions that nurses perform. The Classification includes the interventions that nurses do on behalf of patients, both independent and collaborative interventions, both direct and indirect care. An intervention is any treatment, based upon clinical judgment and knowledge that a nurse
performs to enhance patient/client outcomes. NIC can be used in all settings (from acute care intensive care units, to home care, to hospice, to primary care) and all specialties (from critical care to ambulatory care and long term care) (Bulechek, Butcher, & McCloskey Dochterman, 2008).

**Interventions for Treatment of IV Extravasations with Hyaluronidase**

These interventions selected from Bulechek, Butcher, and McCloskey Dochterman (2008) provide a good match with the focus of the guideline. They were selected because they are associated with the treatment of IV extravasations with hyaluronidase.

- **Skin Surveillance** - Collection and analysis of patient data to maintain skin and mucous membrane integrity.
- **Medication Administration: Intradermal** - Preparing and giving medications via the intradermal route.
- **Medication Administration: Subcutaneous** - Preparing and giving medications via the subcutaneous route.
- **Pain Management** - Alleviation of pain or a reduction in pain to a level of comfort that is acceptable to the patient.
- **Teaching: Prescribed Medication** - Preparing a patient to safely take prescribed medications and monitor for their effects.
- **Incident Reporting** - Written and verbal reporting of any event in the process of patient care that is inconsistent with desired patient outcomes or routine operations of the health care facility.

**Interventions to Prevent IV Extravasations**

These are the interventions associated with the prevention of IV extravasations.

- **Risk Identification** - Analysis of potential risk factors, determination of health risks, and prioritization of risk reduction strategies for an individual or group.
- **Intravenous (IV) Therapy** - Administration and monitoring of intravenous fluids and medications.
- **Total Parenteral Nutrition (TPN) Administration** - Preparation and delivery of nutrients intravenously and monitoring of patient responsiveness.
- **Venous Access Device (VAD) Maintenance** - Management of the patient with prolonged venous access via tunneled and non-tunneled (percutaneous) catheters, and implanted ports.
- **Surveillance: Safety** - Purposeful and ongoing collection and analysis of information about the patient and the environment for use in promoting and maintaining patient safety.

**Additional Optional Interventions**

These are interventions that apply only to some situations and allow the nurse to further tailor the plan of care.
Hyaluronidase for Treatment of Intravenous Extravasations

Evidence-Based Guideline

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EVALUATION OF PROCESS AND OUTCOMES

Process Indicators

Process Indicators are those interpersonal and environmental factors that can facilitate the use of a guideline.

One process indicator that can be assessed with a sample of nurses and licensed independent providers is knowledge about IV extravasations. The IV extravasations Knowledge Assessment Test (See Appendix B) should be assessed before and following the education of staff regarding use of this guideline.

The same sample of nurses and licensed independent providers for whom the Knowledge Assessment test was given should also be given the Process Evaluation Monitor (See Appendix C) approximately one month following his/her use of the guideline. The purpose of this monitor is to determine his/her understanding of the guideline and to assess the support for carrying out the guideline.

Other process indicators can be used to evaluate the support and use of the guideline. For example, one method is to use chart audits to evaluate the inclusion and use of recommended assessment or evaluation forms.

Outcome Indicators

Outcome indicators are those expected to change or improve from consistent use of the guideline. The major outcome indicators that should be monitored over time are:

Baseline Documentation of Extravasation Event

See assessment criteria page 10 of this guideline (Evidence Grade = B: Montgomery et al., 1999).
Use of IV Staging Protocol to Assess Extent of Extravasation

See assessment criteria page 11 of this guideline (Evidence Grade = B: Montgomery et al., 1999).

Time from Extravasation to Treatment

Timely administration is a key factor in achieving positive results; hyaluronidase should be administered within 1-2 hours (Evidence Grade = B: Montgomery et al., 1999).

Ongoing Documentation of Extravasation Event

See assessment section page 11 of this guideline (Evidence Grade = B: Montgomery et al., 1999).

Incidence, Degree, Cause and Corrective Action Taken for Each Extravasation should be Aggregated, Analyzed, and Performance Improvement Planned

Details of all extravasations should be audited documenting the injury including the date, time, needle size, dimensions of the injury, drug that extravasated, time from extravasation to treatment (Evidence Grade = D: Infusion Nurses Society, 2006).

Any extravasation rated greater than a stage 2 should be reported as an unusual occurrence according to institutional policies (Evidence Grade = D: Infusion Nurses Society, 2006).

Extravasations of vesicant medications should be considered sentinel events, with proper documentation and root cause analysis (Evidence Grade = D: Infusion Nurses Society, 2006).

Extravasation rates are calculated by:

\[
\text{Number of Extravasation Incidents} \times 100 = \% \text{ extravasations} \\
\text{Total number of IV catheters}
\]

(Evidence Grade = D: Infusion Nurses Society, 2006).

Morbidities

Patient morbidities should be followed until resolved or static (Evidence Grade = B: Montgomery et al., 1999).

- Pain
- Impaired circulation
- Disfigurement
- Limited mobility
- Loss of function
- Tissue necrosis and ulceration (Evidence Grade = C: Khan & Holmes, 2002).
The Hyaluronidase for IV Extravasations Guideline monitors described in Appendix C are to be used for monitoring and evaluating the usefulness of the hyaluronidase guideline in improving outcomes of patients with IV extravasations.

Nursing Outcomes Classification

The Nursing Outcomes Classification (NOC) is a standardized classification of patient/client outcomes developed to evaluate the effects of nursing interventions. A nursing-sensitive outcome is a measurable individual, family, or community state, behavior or perception that is responsive to nursing interventions. The outcomes are developed for use in all settings and can be used across the care continuum to follow patient response throughout an illness episode or over an extended period of care (Moorhead, Johnson, Maas & Swanson, 2008).

Suggested Outcomes

These outcomes selected from Moorhead, Johnson, Maas, and Swanson (2008) are closely related to the guideline and may be useful in measuring effectiveness for individual patients:

1101 **Tissue Integrity: Skin and mucous Membranes** - Structural intactness and normal physiological function of skin and mucous membranes.
2301 **Medication Response** - Therapeutic and adverse effects of prescribed medication.
0416 **Tissue Perfusion: Cellular** - Adequacy of blood flow through the vasculature to maintain function at the cellular level.
0407 **Tissue Perfusion: Peripheral** - Adequacy of blood flow through the small vessels of the extremities to maintain tissue function.
0401 **Circulation Status** - Unobstructed, unidirectional blood flow at an appropriate pressure through large vessels of the systemic and pulmonary circuits.
2102 **Pain Level** - Severity of observed or reported pain.
1808 **Knowledge: Medication** - Extent of understanding conveyed about the safe use of medication.

Additional Optional Outcomes

These are other possible outcomes that may be useful:

1902 **Risk Control** - Personal actions to prevent, eliminate, or reduce modifiable health threats.
1908 **Risk Detection** - Personal actions to identify personal health threats.
0917 **Neurological Status: Peripheral** - Ability of the peripheral nervous system to transmit impulses to and from the central nervous system.
1843 **Knowledge: Pain Management** - Extent of understanding conveyed about causes, symptoms, and treatment of pain.
1833 **Knowledge: Cancer Management** - Extent of understanding conveyed about cause, type, progress, symptoms, and treatment of cancer.
Wound Healing: Secondary Intention - Extent of regeneration of cells and tissues in an open wound.

Pain Control - Personal actions to control pain.

Pain Disruptive Effects - Severity of observed or reported disruptive effects of chronic pain on daily functioning.

Mobility - Ability to move purposefully in own environment independently with or without assistive device.

Joint Movement - Active range of motion of all joints with self-initiated movement.

Client Satisfaction: Safety - Extent of positive perception of procedures, information and nursing care to prevent harm or injury.

Permission to use Nursing Outcomes Classification (NOC) was obtained through Mosby, Elsevier Health Sciences (http://www.us elsevierhealth.com/).
APPENDIX A
IV EXTRAVASATION ASSESSMENT TOOLS

Appendix A contains examples of assessment tools, and forms to use in assessment of patient IV extravasations. The purpose of the tool and instruction for use accompany each tool or form. Tools, and forms in Appendix A are:

- A1. Table: Chemotherapy agents at high risk for injury with IV extravasation
- A2. Table: Non-chemotherapeutic agents at high risk for injury with IV extravasation
- A3. Table: Distinguishing an IV extravasation from other conditions
- A4. Examples of staging scales for IV extravasations
- A5. Examples of clinical algorithms for IV extravasations
- A6. Examples of documentation records for IV extravasations
## APPENDIX A1.
CHEMOTHERAPY AGENTS AT HIGH RISK FOR INJURY WITH IV EXTRAVASATION

**Purpose:** To determine the risk of tissue necrosis with extravasation by chemotherapy medications.

**Instructions:** This table can be used by nurses and licensed independent providers to identify medications at highest risk for causing tissue necrosis when extravasated. It may be useful for determining if treatment is indicated.

### Table A1. Chemotherapy agents at high risk for injury with IV extravasation

<table>
<thead>
<tr>
<th>Vesicants</th>
<th>Irritants or Possible Irritants*</th>
<th>Nonvesicants with Potential to Cause Irritation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Binding</td>
<td>• Carboplatin**</td>
<td>• Asparaginase</td>
</tr>
<tr>
<td>• Dactinomycin</td>
<td>• Carmustine</td>
<td>• Bleomycin</td>
</tr>
<tr>
<td>• Daunorubicin</td>
<td>• Cisplatin (&gt;0.5 mg/ml &amp; &gt; 20 ml)**</td>
<td>• Bortezomib</td>
</tr>
<tr>
<td>• Doxorubicin</td>
<td>• Cyclophosphamide</td>
<td>• Cladribine</td>
</tr>
<tr>
<td>• Epirubicin</td>
<td>• Da carbazine</td>
<td>• Cytarabine</td>
</tr>
<tr>
<td>• Idarubicin</td>
<td>• Docetaxel**</td>
<td>• Etoposide phosphorate</td>
</tr>
<tr>
<td>• Mechlorethamine</td>
<td>• Etoposide</td>
<td>• Etoposide</td>
</tr>
<tr>
<td>• Mitomycin</td>
<td>• Fluorouracil</td>
<td>• Cladribine</td>
</tr>
<tr>
<td>Non-DNA Binding</td>
<td>• Ifosfamide</td>
<td>• Cytarabine</td>
</tr>
<tr>
<td>• Vinblastine</td>
<td>• Irinotecan**</td>
<td>• Etoposide phosphorate</td>
</tr>
<tr>
<td>• Vincristine</td>
<td>• Oxaliplatin**</td>
<td>• Gemcitabine</td>
</tr>
<tr>
<td>• Vinorelbine</td>
<td>• Melphalan</td>
<td>• Interleukin-2</td>
</tr>
<tr>
<td></td>
<td>• Mitoxantrone</td>
<td>• Methotrexate</td>
</tr>
<tr>
<td></td>
<td>• Paclitaxel**</td>
<td>• Pemetrexed</td>
</tr>
<tr>
<td></td>
<td>• Paclitaxel**</td>
<td>• Thiotepa</td>
</tr>
<tr>
<td></td>
<td>• Streptozocin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Teniposide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Topotecan**</td>
<td></td>
</tr>
</tbody>
</table>

* Any agent extravasated in high enough concentrations or volume may be an irritant
** There have been few reports of these agents acting as irritants, but no clear evidence.
Evidence Grade = B: COG, 2007; European Oncology Nursing Society, 2007; Wengström & Margulies, 2008. Evidence Grade = D; Taketomo, Hodding, & Kraus, 2010.
APPENDIX A2
NON-CHEMOTHERAPEUTIC AGENTS AT HIGH RISK FOR INJURY WITH IV EXTRAVASATION

**Purpose:** To determine the risk of tissue necrosis with extravasation by non-chemotherapeutic agents.

**Instructions:** This list can be used by nurses and licensed independent providers to identify non-chemotherapy medications and blood products at highest risk for causing tissue necrosis when extravasated. It may be useful for determining if treatment is indicated.

**Table A2.** Non-chemotherapeutic agents at high risk for injury with IV extravasation

<table>
<thead>
<tr>
<th>Hyperosmolar Solutions</th>
<th>Ischemia-Inducing Agents</th>
<th>Alkaline Agents</th>
<th>Poorly Water-Soluble Agents</th>
<th>Miscellaneous Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium chloride*</td>
<td>Dopamine*</td>
<td>Amphotericin B</td>
<td>Diazepam</td>
<td>Aminophylline</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>Dobutamine*</td>
<td>Etomidate</td>
<td>Digoxin</td>
<td>Blood products</td>
</tr>
<tr>
<td>Contrast media*</td>
<td>Epinephrine*</td>
<td>Methylene blue</td>
<td>Nitroglycerin</td>
<td>Epoprostenol</td>
</tr>
<tr>
<td>Dextrose (&gt;10%)*</td>
<td>Norepinephrine*</td>
<td>Sodium bicarbonate</td>
<td>Phenytoin*</td>
<td>Gentamicin*</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Vasopressin*</td>
<td>Sodium thiopental</td>
<td></td>
<td>Magnesium</td>
</tr>
<tr>
<td>Mannitol (≥15%)</td>
<td></td>
<td></td>
<td></td>
<td>Platelets</td>
</tr>
<tr>
<td>Nafcillin*</td>
<td></td>
<td></td>
<td></td>
<td>Promethazine*</td>
</tr>
<tr>
<td>Penicillin*</td>
<td></td>
<td></td>
<td></td>
<td>Propofol*</td>
</tr>
<tr>
<td>Potassium chloride*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total parenteral nutrition*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tromethamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reported to cause tissue necrosis in one or more source

### APPENDIX A3.

**DISTINGUISHING AN IV EXTRAVASATION FROM OTHER CONDITIONS**

**Purpose:** To be used to distinguish an IV extravasation from other conditions.

**Instructions:** This is a table comparing extravasation characteristics to those of like conditions. It may be useful for determining if the injury is extravasation or another condition.

**Table A3:** Distinguishing an IV extravasation from other conditions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Flare reaction</th>
<th>Vessel irritation</th>
<th>Venous shock</th>
<th>Extravasation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>Itchy blotches or hives; pain and</td>
<td>Aching and tightness</td>
<td>Muscle wall of the blood vessel in spasm</td>
<td>Pain and burning are common at the injection site, stinging may occur during the infusion</td>
</tr>
<tr>
<td></td>
<td>burning uncommon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coloration</td>
<td>Raised red streak, blotches or “hive-like” erythema along the vessel; diffuse or irregular pattern</td>
<td>Erythema or dark discoloration along vessel</td>
<td></td>
<td>Erythema around area of needle or around the venipuncture site</td>
</tr>
<tr>
<td>Timing</td>
<td>Usually appears suddenly and dissipates within 30-90 minutes</td>
<td>Usually appears within minutes after an injection. Coloration may only appear later in the process.</td>
<td>Usually appears right after an injection</td>
<td>Symptoms start to appear right after injection, symptoms endure</td>
</tr>
<tr>
<td>Swelling</td>
<td>Unlikely</td>
<td>Unlikely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood return</td>
<td>Usually, but not always intact</td>
<td>Usually, but not always intact</td>
<td>Often absent</td>
<td>Usually absent or sluggish</td>
</tr>
</tbody>
</table>

APPENDIX A4.
EXAMPLES OF STAGING SCALES FOR IV EXTRAVASATION

Purpose: To be used to assess IV site at baseline, frequent intervals and/or upon extravasation.

Instructions: These are examples of staging scales that can be used by nurses and licensed independent providers to assess IV sites and grade extravasation injuries. They may be useful for determining if treatment is indicated.

Example A4a. Extravasation staging scale from Infusion Nurses Society

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Skin blanched</td>
</tr>
<tr>
<td></td>
<td>Edema &lt; 1 inch in any direction</td>
</tr>
<tr>
<td></td>
<td>Cool to touch</td>
</tr>
<tr>
<td></td>
<td>With or without pain</td>
</tr>
<tr>
<td>2</td>
<td>Skin blanched</td>
</tr>
<tr>
<td></td>
<td>Edema 1-6 inches in any direction</td>
</tr>
<tr>
<td></td>
<td>Cool to touch</td>
</tr>
<tr>
<td></td>
<td>With or without pain</td>
</tr>
<tr>
<td>3</td>
<td>Skin blanched, translucent</td>
</tr>
<tr>
<td></td>
<td>Gross edema &gt;6 inches in any direction</td>
</tr>
<tr>
<td></td>
<td>Cool to touch</td>
</tr>
<tr>
<td></td>
<td>Mild or moderate pain</td>
</tr>
<tr>
<td></td>
<td>Possible numbness</td>
</tr>
<tr>
<td>4</td>
<td>Skin blanched, translucent</td>
</tr>
<tr>
<td></td>
<td>Skin tight, leaking</td>
</tr>
<tr>
<td></td>
<td>Skin discolored, bruised, swollen</td>
</tr>
<tr>
<td></td>
<td>Gross edema &gt;6 inches in any direction</td>
</tr>
<tr>
<td></td>
<td>Deep pitting tissue edema</td>
</tr>
<tr>
<td></td>
<td>Circulatory impairment</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe pain</td>
</tr>
<tr>
<td></td>
<td>Infiltration of any amount of blood product, irritant or vesicant</td>
</tr>
</tbody>
</table>

Evidence Grade = D: Infusion Nurses Society, 2006.
See Groll et al., 2010 for psychometric properties.
Copied with permission from Infusion Nurses Society.
Example A4b. IV extravasation staging scale from University of Iowa Children’s Hospital

**STAGING OF IV INFILTRATIONS/EXTRAVASATIONS**
Symptoms do not necessarily need to all be present to assign rating. Infiltration should be staged according to the most severe presenting indicator. Purpose of scale is to identify differences and generate interventions by nurses and Licensed Independent Practitioners (LIP).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No redness, pain, edema, blanching, tenderness or drainage. Flushes with ease</td>
<td>No intervention needed.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Mild redness Mild edema Flushes with ease Skin warm to touch Good distal pulses 1-2 second distal capillary refill</td>
<td>Check tape/IV securement Elevate extremity Consider using alternative site for meds and IV fluids</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Persistent mild redness Persistent mild edema Flushes with difficulty Pain at site Skin blanched Skin cool to touch Good distal pulses 1-2 second distal capillary refill</td>
<td>Stop the infusion At discretion of nurse, may: Get help, FAST, by notifying LIP and activating other resources Attempt to aspirate back any residual fluid from the existing catheter. Remove IV if not needed for treatment/antidote administration Elevate extremity Treatment: At LIP discretion, may opt to treat in some cases If IV is still in place, remove it</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderate edema Moderate redness Skin blanched Flushes with difficulty Pain at site mild-moderate Skin cool to touch Good distal pulses 1-3 second distal capillary refill</td>
<td>Stop the infusion Anticipate treatment: Get help, FAST: By notifying LIP and activating other resources Attempt to aspirate back any residual fluid from the existing catheter. Remove IV if not needed for treatment/antidote administration Elevate extremity Treatment based on LIP discretion If IV is still in place, remove it</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Moderate to severe and/or pitting edema Persistent redness, discoloration, bruising Skin blanched Pain at site moderate-severe Skin cool to touch Skin breakdown or necrosis Decreased or absent distal pulses &gt; 3 second distal capillary refill Infiltration of any amount of blood product, irritant, or vesicant</td>
<td>Remove IV if not needed for treatment/antidote administration Elevate extremity Treatment based on LIP discretion If IV is still in place, remove it</td>
</tr>
</tbody>
</table>

Copied with permission from: University of Iowa Hospital and Clinics, Children’s and Women’s Services, (2011). Standard of Practice: N-CWS-PEDS-08.130.
APPENDIX A5.
EXAMPLES OF CLINICAL ALGORITHMS FOR IV EXTRAVASATIONS

**Purpose:** To be used to assess intravenous (IV) extravasations and determine the course of treatment

**Instructions:** These are examples of clinical algorithms that can be used by nurses and licensed independent providers to assess IV extravasations. They may be useful for determining appropriate evidence-based treatment.

**Example A5a.** Clinical algorithm for IV extravasations adapted from European Oncology Nursing Society

Adapted from European Oncology Nursing Society, 2007. Evidence Grade = B.
**Example A5b.** Clinical algorithm for IV extravasations from University of Iowa Children’s Hospital

**IV Extravasation**

- **Stage 0**
  - No Extravasation

- **Stage 1 or 2**
  - Assess
  - Stop infusion
  - Attempt to aspirate back any residual fluid from existing catheter
  - Remove peripheral IV (PIV) if not needed for antidote treatment
  - Elevate

- **Stage 3 or 4, any blood or vesicant agent**
  - Assess
  - Stop infusion
  - Attempt to aspirate back any residual fluid from existing catheter
  - Remove peripheral IV (PIV) if not needed for antidote treatment
  - Elevate

**Get help! FAST**

- Notify provider (LIP)
- Activate other resources

**Disperse and Dilute:**
- See indications hyaluronidase
- Discontinue PIV
- Administer per procedure
- Apply heat per procedure
- Manage pain

**Documentation**
- Digital Photographs to electronic medical record
- PSN report (required if > Stage 2, otherwise optional)
- Patient education

**Extravasation resolved**

--- Optional step, at discretion of the provider

Copied with permission from: University of Iowa Hospital and Clinics, Children’s and Women’s Services, (2010).

Standard of Practice: N-CWS-PEDS-08.130.

**Consult?**

**Treat?**

**Localize and Neutralize:**
- See indications/antidotes
- Administer per procedure
- Discontinue PIV
- Apply cold per procedure
- Manage pain

**As needed for further treatments:**
- Pharmacy
- Wound care specialist (dressings)
- Burn treatment team
- Surgeons (consider saline washout, or for large extravasations, compartment syndrome, severe pain or failed treatment)
- Physical Therapy depending on location
Example A5c. Clinical algorithm for IV extravasations from North Trent Cancer Network-Extravasation Guidelines V4

Note: Authors report that other treatments are also available for Group B extravasations but not used in their Network, (personal communication, Judith Bird, North Trent Cancer Network, October, 2011).

Copied with permission from North Trent Cancer Network
© North Trent Cancer Network 2006
APPENDIX A6.
EXAMPLES OF DOCUMENTATION RECORDS FOR IV EXTRAVASATIONS

**Purpose:** To be used to document IV extravasations.

**Instructions:** This is an example of tool that can be used by nurses and licensed independent providers to document IV extravasations.

**Example A6a.** Documentation record for IV extravasations from European Oncology Nursing Society

![Documentation record for IV extravasations](image)

---

Supplement for Mader et al., Extravasation of Cytotoxic Agents © Springer-Verlag Wien 2003
### Extravasation of cytotoxic agents – Documentation (II)

**Extravasation recognised:**
- Date [__|__|__ | __|__ |__]  
- Time of day: .......
- Day month year

1. **During administration**
2. **Immediately after administration**
3. **..... hours after administration**
4. **..... days after administration**

**Measures:**
- Aspiration of cytotoxic drug possible:  
  - ○ Yes  ○ No
- Recommended general and substance specific measures taken:  
  - ○ Yes  ○ No
- Additional measures taken: .................................................................
  .................................................................

**Risk factors that may influence wound healing (for example, diabetes mellitus):**
- ...........................................................................................................
  ...........................................................................................................

**Information for/ instructions to patient:**
- (Plastic) surgeon consulted:  
  - ○ Yes  ○ No
- Next control appointment:  
  - [__|__|__ | __|__ |__]  
  - Day month year
  - Time: .......
  - Ward: .......

**Documented by:** .................................................................
- Name in capital letters, please

**E-mail:** .................................................................

**Affiliation:** .................................................................

---

Supplement for Mader et al., Extravasation of Cytotoxic Agents. © Springer-Verlag Wien 2005
## Extravasation of cytotoxic agents – Documentation (III)

<table>
<thead>
<tr>
<th>Date</th>
<th>Paraph of doctor</th>
</tr>
</thead>
</table>

### Symptoms after extravasation:
- Pain (burning, stinging)
- Oedema
- Erythema
- Blisters
- Discolouration
- Induration
- Functional impairment
- Ulceration
- Necrosis
- Exudation
- Formation of eschar
- Infection
- Complete healing

### Extent of extravasation:
- Two widest diameters in cm
- Measurements

### Conservative measures
- Surgical measures:
  - Excision
  - Transplantation

---

Evidence Grade = B: European Oncology Nursing Society, 2007.  
Example A6b. Documentation record for IV extravasations from European Oncology Nursing Society

<table>
<thead>
<tr>
<th>Extravasation of anthracycline</th>
<th>Observation and prescription form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Height/Weight <strong><strong><strong>/</strong></strong></strong></td>
</tr>
<tr>
<td>Date of birth:</td>
<td>Surface (m²) ______</td>
</tr>
<tr>
<td>Telephone number:</td>
<td></td>
</tr>
<tr>
<td>Time/day</td>
<td>0-6 hrs Day</td>
</tr>
<tr>
<td>Observation Date:</td>
<td></td>
</tr>
<tr>
<td>Observation Time:</td>
<td></td>
</tr>
<tr>
<td>Time of extravasation:</td>
<td></td>
</tr>
<tr>
<td>Location of extravasation:</td>
<td></td>
</tr>
<tr>
<td>Describe IV access from which</td>
<td></td>
</tr>
<tr>
<td>Extravasation occurred:</td>
<td></td>
</tr>
<tr>
<td>Aspiration on catheter (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Size of the affected area (cm x cm)</td>
<td>x x x x x x x x x</td>
</tr>
<tr>
<td>Name of anthracycline diluent</td>
<td></td>
</tr>
<tr>
<td>Amount of fluid extravasated</td>
<td>mL</td>
</tr>
<tr>
<td>Amount of anthracycline extravasated</td>
<td>Mg</td>
</tr>
<tr>
<td>Local ice treatment (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Patient at least 15 min before use?</td>
<td>Mg</td>
</tr>
<tr>
<td>Other local treatment (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>Describe symptoms listed below using yes/no or use CTC grades none, mild, moderate, severe</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>Local swelling</td>
<td></td>
</tr>
<tr>
<td>Local tenderness</td>
<td></td>
</tr>
<tr>
<td>Local blistering</td>
<td></td>
</tr>
<tr>
<td>Local necrosis</td>
<td></td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td></td>
</tr>
<tr>
<td>Skin atrophy</td>
<td></td>
</tr>
<tr>
<td>Impaired limb function</td>
<td></td>
</tr>
<tr>
<td>Dequamation</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
</tr>
<tr>
<td>Day 1 and 2: 1000 mg/m², Day 3: 500 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Savene™ infusion (mg total)</td>
<td></td>
</tr>
<tr>
<td>Start time of Savene™ infusion</td>
<td></td>
</tr>
<tr>
<td>Stop time of Savene™ infusion</td>
<td></td>
</tr>
<tr>
<td>Signature doctor</td>
<td></td>
</tr>
<tr>
<td>Signature nurse</td>
<td></td>
</tr>
</tbody>
</table>


Additional comments:

Evidence Grade = B: European Oncology Nursing Society, 2007.
**Example A6c.** Documentation record for IV peripheral IV extravasations from North Trent Cancer Network

<table>
<thead>
<tr>
<th>North Trent Cancer Network</th>
<th>Extravasation reporting form for peripheral cannula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s name</td>
<td>Hospital Number</td>
</tr>
<tr>
<td>D.O.B</td>
<td>Male</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incident details</th>
<th>Drug involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>When noticed (e.g. on occurrence, at OPA, readmission)</td>
<td></td>
</tr>
<tr>
<td>Date of extravasation</td>
<td>Time</td>
</tr>
<tr>
<td>Dose of chemo</td>
<td>In (total volume)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of administration</th>
<th>Circle</th>
<th>IV infusion via volumetric pump</th>
<th>Infusor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus at side arm of infusion</td>
<td>Free flow IV infusion</td>
<td>Bolus to cannula</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimate of amount of drug extravasated</th>
<th>OR</th>
<th>amount unknown (circle if not known)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Type of cannula (e.g. insyte, venflon)</th>
<th>Gauge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannulation details (if known):</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>Time</td>
</tr>
<tr>
<td>No. of attempts</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What symptoms of extravasation occurred (circle any):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Y</td>
</tr>
<tr>
<td>Tingling</td>
<td>Y</td>
</tr>
<tr>
<td>Swelling</td>
<td>Y</td>
</tr>
<tr>
<td>Redness</td>
<td>Y</td>
</tr>
<tr>
<td>Itching</td>
<td>Y</td>
</tr>
<tr>
<td>Cold</td>
<td>Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>List any other sign(s) that lead to extravasation being suspected (e.g. absence of infusion flow, syringe resistance, leakage around cannula etc)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Action taken</th>
<th>to be completed by nurse/doctor giving treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Designation</td>
</tr>
<tr>
<td>Attempt made to withdraw solution from site: Yes/ No</td>
<td>Amount withdrawn</td>
</tr>
<tr>
<td>Treatment given (circle ANY used):</td>
<td>Cold pad</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>DMSO</td>
</tr>
<tr>
<td>Other(s) (specify)</td>
<td></td>
</tr>
<tr>
<td>Give reason for any variation from guidelines</td>
<td></td>
</tr>
<tr>
<td>Name of doctor informed:</td>
<td>Time:</td>
</tr>
<tr>
<td>Patient info given: Yes/ No</td>
<td>Reasons if no:</td>
</tr>
<tr>
<td>Follow up arrangements</td>
<td></td>
</tr>
<tr>
<td>Reason for any variation from follow up guidance</td>
<td></td>
</tr>
<tr>
<td>Was referral required to plastic surgeon? Yes/ No</td>
<td>Name of surgeon</td>
</tr>
<tr>
<td>If yes, action taken:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nurse completing form</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Y3 May 2011)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example A6d. Documentation record for IV Central Venous Access Devices IV extravasations from North Trent Cancer Network

![Example A6d](image)

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APPENDIX B
IV EXTRAVASATION KNOWLEDGE ASSESSMENT TEST

Appendix B contains an example of an assessment tool for assessing knowledge of IV extravasations and treatment. The purpose of the tool and instructions are included. Tools, and forms in Appendix B are:

- B1. Hyaluronidase for IV extravasation knowledge assessment test
APPENDIX B1

Purpose: To be used to assess knowledge of hyaluronidase for treatment of IV extravasations.

Instructions: This is a tool that can be used to assess nurse’s and licensed independent provider’s knowledge of hyaluronidase for IV extravasations.

The individual, who will be managing use of this evidence-based guideline and coordinating education of staff, should be the only one who has access to this test key. Following proper education with regard to hyaluronidase for intravenous (IV) extravasations, each nurse or licensed independent provider should be given an opportunity to take this test. Use this test as a learning tool only. Please have each nurse or licensed independent provider take this test without the key present, and once he/she is done, let them code how many questions they answered correctly and incorrectly. Guidance in determining why he/she answered as they did can also be part of the learning process.

HYALURONIDASE FOR IV EXTRAVASATION KNOWLEDGE ASSESSMENT TEST KEY

1. B
2. ABDE
3. B
4. E
5. C
6. C
7. A
8. B
9. C
10. E
HYALURONIDASE FOR IV EXTRAVASATION KNOWLEDGE ASSESSMENT TEST

Please answer the following questions to assess your intravenous (IV) extravasation knowledge.

1. **An IV infiltration/extravasation is best defined as:**
   A. A localized inflammatory process caused by chemotherapy agents that irritate the veins
   B. The inadvertent leaking of a damaging agent out of the vein and into the surrounding tissue
   C. A raised red streak, blotches or “hive-like” erythema along the vessel
   D. Increased pressure within a limited anatomical space which compromises the circulation and function of tissues within the space.

2. **Of the following patients, mark ALL that are at high risk for an infiltration/extravasation injury:**
   A. A preterm infant receiving parenteral venous nutrition (15% dextrose) through a peripheral IV in a scalp vein
   B. A 4 year-old with spina bifida receiving vancomycin through a peripheral IV in the foot
   C. An 8 year-old with dehydration getting a normal saline bolus through a peripheral IV.
   D. A 10 year-old patient with cancer receiving vincristine through a port.
   E. A 16 year-old patient with a head injury getting contrast for a MRI study.

3. **Which ONE of the following steps is NOT taken when administering hyaluronidase:**
   A. Aspirate residual agent at the site through the existing catheter
   B. Apply firm pressure and massage at the site
   C. Elevate the extremity
   D. Administer hyaluronidase, as soon as possible after the event

4. **Hyaluronidase is administered by what route:**
   A. IV intravascular
   B. SQ subcutaneous
   C. ID intradermal
   D. IV or SQ
   E. SQ or ID

5. **Treatment of an infiltration/extravasation with hyaluronidase is CONTRAINDIATED with which agents:**
   A. Calcium solutions
   B. Vinca Alkaloids
   C. Vasopressors and alpha antagonist
   D. Blood products
   E. It is indicated for all these agents
6. **If you were treating an IV extravasation, where would you administer hyaluronidase?**
   A. Directly at the site
   B. Through the existing catheter only
   C. Around the site but not into existing catheter
   D. Around the site and through the existing catheter

7. **For best outcomes, hyaluronidase should be administered within one to two hours of the extravasation.**
   A. True
   B. False

8. **Administration of hyaluronidase should NOT be repeated for 48 hours, even if the extravasation injury is progressing.**
   A. True
   B. False

9. **The best way to manage pain with extravasations is to:**
   A. Most extravasations are not that painful, apply cold compresses for 15 minutes every hour x 4
   B. Wait and see if an ulcer develops before administering hyaluronidase, avoid painful SQ or ID injections if possible
   C. Administer systemic analgesics and non-pharmacologic comfort measures for mild extravasations and oral or IV opioids for severe extravasations.
   D. Apply topical anesthetic cream for 60 minutes.

10. **An incident/unusual event report should be completed for all the following situations EXCEPT:**
   A. A Stage 1 extravasation that develops an ulcer after 24 hours
   B. A Stage 2 extravasation treated with hyaluronidase
   C. A Stage 3 extravasation that the LIP determines does not need treatment
   D. Extravasation of a vesicant drug
   E. No exceptions, an incident/unusual event report should be completed in all these situations
APPENDIX C

QUALITY AND PERFORMANCE MONITORS FOR IV EXTRAVASATIONS

Appendix C contains examples of quality and performance measures to use in monitoring intravenous (IV) extravasations. The purpose of the monitor and instruction for use accompany each tool or form. Tools, and forms in Appendix C are:

- C1. Example of process evaluation monitor
- C2. Example of outcome monitor for IV extravasations
- C3. Examples of event monitors for IV extravasations
- C4. Example of audit for monitoring IV catheters
- C5. Example of national data base event monitor for IV extravasations
APPENDIX C1
EXAMPLE OF PROCESS EVALUATION MONITOR FOR IV EXTRAVASATIONS

Purpose: To evaluate perceived understanding and support of each nurse or licensed independent provider in carrying out the guideline.

Instructions: PLEASE COPY THE FORM ON THE NEXT PAGE and ask each nurse or licensed independent provider who uses the guideline to complete it approximately one month following his/her initial use of this guideline.

Once the nurses or licensed independent providers who are using the guideline complete this Process Evaluation Monitor, the individual in charge of implementing the guideline should provide feedback to each person who completed a form and offer further education or support as needed. For the 10 questions, please tally up the responses provided by adding up the numbers circled. For example, if Question 1 is answered ‘2’ and Question 2 is answered ‘3’ and Question 3 is answered ‘4’ the nurse’s score for those three questions (2+3+4) equals 9. The total score possible on this monitor is 36, while the lowest score possible is 9. Those who have higher scores on this monitor are indicating that they are well-equipped to implement the guideline, and understand its use and purpose. On the other hand, those who have relatively low scores are in need of more education and support in the use of the guideline.
Example C1. Process evaluation monitor

**Directions:** Please circle the number that best communicates your perception about your use of the *Hyaluronidase for Treatment of Intravenous Extravasations* guideline.

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel knowledgeable to carry out the Hyaluronidase for IV Extravasations guideline.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Implementing the Hyaluronidase for IV Extravasations guideline enhances the quality of nursing care on the unit.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. I feel supported in my efforts to implement the Hyaluronidase for IV Extravasations guideline.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. I feel well prepared to carry out the Hyaluronidase for IV Extravasations guideline with the assistance of the resources provided.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. I am able to identify indications for treatment with Hyaluronidase for IV extravasations.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. I am able to identify and carry out the essential activities of the Hyaluronidase for IV Extravasations intervention.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. I had enough time to learn about the Hyaluronidase for IV Extravasations guideline before it was implemented.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. We are managing IV extravasations better with the use of the guideline.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. The guideline enables me to meet the IV extravasations needs of most patients.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
APPENDIX C2
EXAMPLE OF OUTCOMES MONITOR FOR IV EXTRAVASATIONS

**Purpose:** Identify outcomes to evaluate the incidence of IV extravasations for performance improvement.

**Instructions:**
Extravasation outcomes should be calculated quarterly and benchmarked yearly against institutional and comparative institutions performances.

**Example C2. Outcomes monitor for IV extravasations**

**Directions:** Please place the appropriate rate next to each outcome for the quarter.

<table>
<thead>
<tr>
<th>Outcome 1: Extravasation rate % =</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
</tr>
</thead>
<tbody>
<tr>
<td># of extravasation incidents X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # of IV catheters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome 2: Treatment rate % =</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
</tr>
</thead>
<tbody>
<tr>
<td># treated with hyaluronidase X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number extravasations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome 3: Morbidity rate % =</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # with morbidity X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number extravasations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity 1:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># with morbidity X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number extravasations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity 2:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># with morbidity X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number extravasations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># with morbidity X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number extravasations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Calculate total and each separate

<table>
<thead>
<tr>
<th>Outcome 4: Morbidity rate % by treatment vs. no treatment</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # treated X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # treated with morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # treated without morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # treated without morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # not treated X 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # not treated with morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # not treated without morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary/ Comments:**

Year 1: ________________________________

Year 2: ________________________________
APPENDIX C3
EXAMPLES OF EVENT MONITORS FOR IV EXTRAVASATIONS

**Purpose:** To evaluate the degree, cause and corrective action taken for each IV extravasation event for performance improvement.

**Example C3a. Event monitor for IV extravasations**

**Instructions:** This form should be completed for every extravasation event requiring interventions and maintained by the organizations quality committee.

**Directions:** **TO USE THE FORM:** Place the appropriate criteria key next to each separate outcome for each patient assessment. We have provided a total of 8 boxes, which represent the first eight events.

<table>
<thead>
<tr>
<th>Criteria Key</th>
<th>Event 1</th>
<th>Event 2</th>
<th>Event 3</th>
<th>Event 4</th>
<th>Event 5</th>
<th>Event 6</th>
<th>Event 7</th>
<th>Event 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y=Yes/met criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=No/criteria not met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J=Justified Variation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Outcome 1:** Identify extravasations that should be treated with hyaluronidase.

**Source:** Documented in medical record.

**Indicators:**
- Stage of extravasation
- Medication administered
- Volume of extravasate
- Dimensions of injury
- LIP notified

**Outcome 2:** Administer hyaluronidase within two hours if indicated.

**Source:** Documentation in medical record.

**Indicators:**
- Time of event
- Time of administration
- Nursing interview
- Barriers to treatment
<table>
<thead>
<tr>
<th>Event 1</th>
<th>Event 2</th>
<th>Event 3</th>
<th>Event 4</th>
<th>Event 5</th>
<th>Event 6</th>
<th>Event 7</th>
<th>Event 8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome 3:</strong>&lt;br&gt;Integrity of the skin is restored</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indicators:&lt;br&gt;Normal physical exam&lt;br&gt;Skin color&lt;br&gt;Temperature&lt;br&gt;Sensory loss&lt;br&gt;Range of motion&lt;br&gt;Pain&lt;br&gt;Circulation&lt;br&gt;Absence of scarring or disfigurement&lt;br&gt;Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome 4:</strong>&lt;br&gt;Patient/family communication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Source:</strong> Patient family interview&lt;br&gt;<strong>Indicators:</strong>&lt;br&gt;Did you know your child’s IV extravasated?&lt;br&gt;Do you understand what happened?&lt;br&gt;Do you know what was done to treat it?&lt;br&gt;Did you get information from the team when it happened?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome 5:</strong>&lt;br&gt;Appropriate evaluation and action for sentinel events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Source:</strong> Patient Medical record&lt;br&gt;<strong>Indicators:</strong>&lt;br&gt;Unusual incident report&lt;br&gt;Criteria for sentinel event met/unmet&lt;br&gt;Actions taken</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example C3b. Event monitor for IV extravasations from North Trent Cancer Network

North Trent cancer network

Venous extravasation follow up documentation record

Record of follow up for all extravasations where ongoing surveillance is required

Patient's name________________ Hospital Number________________
D.O.B.________________ Consultant________________ Phone contact:________________
Address:________________

Attach a copy of the original extravasation form to this record if it is available. If not available complete the following information on patients first surveillance visit:

Date of extravasation__/__/____ Ward/Dept where incident occurred________________
Drug involved________________ Was a photograph taken? Yes No

Location of extravasation: (Complete box below)

[Diagram of a hand with options for left, right, front, and back]

Assessment record

Date of assessment__/__/____ Method (e.g. phone, attended ward/dept)________________
Person completing assessment________________ Ward/Dept________________

Description of extravasation site: Measurement of area (cm): _______ by _______

Is there any redness/discolouration  Yes No  Skin breakdown  Yes No

Blistering  Yes No  Blanching  Yes No

Changes in sensation  Yes No (if yes, describe)

Functional changes (e.g. difficulty with grip, movement)  Yes No (if yes, describe)

Pain - 0 to 10 (0 = no pain, 10 = unbearable)________
Action taken:

Next review date (if required)__/__/____
Review method and location (e.g. phone, ward/dept)

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APPENDIX C4
EXAMPLE OF AUDIT FOR MONITORING IV CATHETERS

**Purpose:** This is an example of a data base to evaluate the natural life of an IV catheter and identify IV complications.

**Instructions:** This example can be used for developing a data base for audits.

**Example C4. Audit for monitoring IV catheters from The National Extravasation Information Service**

**Directions:** For each catheter enter the available data into the database.

<table>
<thead>
<tr>
<th>Your Email Address</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Your Name</td>
<td></td>
</tr>
<tr>
<td>Hospital Centre</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Cannulated</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Cannula</td>
<td></td>
</tr>
<tr>
<td>Make of Cannula</td>
<td></td>
</tr>
<tr>
<td>Person Cannulating</td>
<td></td>
</tr>
<tr>
<td>Ease of Cannulation (on a scale of 1 to 10, where 1 is Very Easy and 10 is Extremely Difficult)</td>
<td></td>
</tr>
<tr>
<td>State of the Veins (on a scale of 1 to 10, where 1 is Very Healthy and 10 is Collapsed)</td>
<td></td>
</tr>
<tr>
<td>No of Attempts at Cannulation</td>
<td></td>
</tr>
<tr>
<td>Cannula finally placed in</td>
<td>Left Arm</td>
</tr>
<tr>
<td>Reason for Cannula Failure</td>
<td>No longer needed</td>
</tr>
<tr>
<td>Patient's Age</td>
<td></td>
</tr>
</tbody>
</table>
Example C4. continued

Observation

[Grade each criterion against the standard scales shown in the table below]
### Example C4. continued

<table>
<thead>
<tr>
<th>Grade</th>
<th>Colour</th>
<th>Feel</th>
<th>Flow</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No discolouration of vein or surrounding area</td>
<td>Fat 'juicy' veins, no pain</td>
<td>Normal</td>
<td>No adverse sensation</td>
</tr>
<tr>
<td>2</td>
<td>Vein looks slightly red</td>
<td>Firm and fixed, no pain</td>
<td>Slower than when started, but not interrupted</td>
<td>Can feel flow through cannula but no discomfort</td>
</tr>
<tr>
<td>3</td>
<td>Vein and surrounding tissue look red +/- inflamed</td>
<td>Tender and irritable. Especially painful on palpation</td>
<td>Partial Flow</td>
<td>Discomfort, but not really painful</td>
</tr>
<tr>
<td>4</td>
<td>Frank phlebitic discolouration of vein and tissues</td>
<td>Sclerotic and fibrous, very painful</td>
<td>No Flow</td>
<td>Painful</td>
</tr>
</tbody>
</table>


Evidence Grade = D: Stanley, 2007

Open accessed from [http://www.extravasation.org.uk/home.html](http://www.extravasation.org.uk/home.html)
APPENDIX C5
EXAMPLE OF NATIONAL DATA BASE EVENT MONITOR FOR IV EXTRAVASATIONS

**Purpose:** This is an example of a national data base to monitor and evaluate trends in IV extravasation events, treatments, and outcomes.

**Instructions:** This example can be used for developing a data base for IV extravasation events.

**Example C5. National data base event monitor from Great Britain**

**Directions:** For each IV extravasation enter the available data into the database.

**Green Card Report - please enter all available details**

<table>
<thead>
<tr>
<th>Field</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Height(m)</td>
<td></td>
</tr>
<tr>
<td>Weight(kg)</td>
<td></td>
</tr>
<tr>
<td>Ethnic Origin</td>
<td>White British</td>
</tr>
<tr>
<td>Drug causing extravasation</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>Given as</td>
<td>Infusion</td>
</tr>
<tr>
<td>Infusion fluid and volume</td>
<td></td>
</tr>
<tr>
<td>Given via</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>22g</td>
</tr>
<tr>
<td>Over</td>
<td>mins</td>
</tr>
<tr>
<td>The above drug formed part of course no</td>
<td>in the following regime</td>
</tr>
<tr>
<td>Is the Patient on any of the following Therapies?</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Antiplatelets</td>
<td></td>
</tr>
<tr>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Hormone Therapy</td>
<td></td>
</tr>
<tr>
<td>Antifibrinolytics</td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td>Has the patient received I.V antibiotics in the last 3 months? Yes/No</td>
<td>Yes</td>
</tr>
<tr>
<td>If YES please specify</td>
<td></td>
</tr>
<tr>
<td>Has the patient had previous :- Drug Hypersensitivity/Phlebitis</td>
<td>Drug Hypersensitivity Phlebitis</td>
</tr>
</tbody>
</table>
Example C5. continued

Were the drugs being administered via a pump or syringe driver?  Yes ☐  No ☐

If YES please indicate model

Time of Cannulation

No of attempts at cannulation

Ease of Cannulation

Other Method of Administration □  □  □  Other (please specify)

Details of Extravasation Treatment (Drug, Dose, Procedure)

Did the Patient experience any of the following prior to or after the suspected extravasation?

<table>
<thead>
<tr>
<th></th>
<th>Prior</th>
<th>Post</th>
<th>Time Post Extravasation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Tingling</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Swelling</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Redness/Flare</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Itching</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Cold</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Example C5. continued

| Date of Extravasation |  |
| Time of Extravasation |  |
| Acute extravasation treatment started at |  |

**THIS SECTION IS NOT COMPULSORY**

<table>
<thead>
<tr>
<th>Contact Name for Further Details:</th>
<th>Dr</th>
<th>Nurse</th>
<th>Pharmacist</th>
<th>Tel no</th>
<th>Email</th>
</tr>
</thead>
</table>

**Does the patient suffer from any of the following possible contributary factors?**

- Raynaud's Disease [ ]
- Diabetes [ ]
- Peripheral Vascular Disease [ ]
- Lymphoedema [ ]

**Has the patient had either of the following in the last month, to the affected side?**

- Surgery [ ] Date [ ]
- Radiotherapy [ ] Date [ ]

**Additional Comments:**

[ ]

**Was the patient able to communicate adequately in English?** Yes [ ] No [ ]

If not, please give reason [ ]


Open accessed from [http://www.extravasation.org.uk/home.html](http://www.extravasation.org.uk/home.html)
APPENDIX D
IMPLEMENTATION TOOLS FOR IV EXTRAVASATIONS

Appendix D contains additional implementation tools that may be useful for translating the *Hyaluronidase for Treatment of Intravenous Extravasations Guideline* into practice.

- D1. Table: Hyaluronidase products
- D2. Table: Evidence for the use of hyaluronidase with specific agents
- D3. Table: Dressings for IV extravasation wounds
- D4. Table: Topical treatments for IV extravasation wounds
- D5. Examples of quick reference cards
- D6. Examples of patient information sheets for managing extravasations
APPENDIX D1.
HYALURONIDASE PRODUCTS

**Purpose:** To compare USFDA-approved hyaluronidase products.

**Intended users:** Nurses and licensed independent practitioners

Table D1. Hyaluronidase Products

<table>
<thead>
<tr>
<th>Drug Name Manufacturer, (USFDA-approval date)</th>
<th>Strength</th>
<th>Source</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphadase® by Amphastar Pharmaceuticals (10/26/2004)</td>
<td>Solution: 150 units/ml</td>
<td>Purified bovine testicular hyaluronidase</td>
<td>Contains ≤ 0.1 mg/ml of thimerosal (mercury derivative).</td>
</tr>
<tr>
<td>Hydase® by PrimaPharm (10/25/05)</td>
<td>Solution: 150 units/ml</td>
<td>Purified bovine testicular hyaluronidase</td>
<td>Note: Product was discontinued by the manufacturer (4/2009).</td>
</tr>
<tr>
<td>Hylenex® Recombinant (rHUPH20) by Halozyme Therapeutics/ Baxter (12/2/05)</td>
<td>Solution: 150 units/ml</td>
<td>Recombinant human hyaluronidase. Produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing a DNA plasmid encoding for soluble fragment of human hyaluronidase.</td>
<td>Contains no animal derivatives.</td>
</tr>
<tr>
<td>Vitrase® by ISTA Pharmaceuticals (5/5/2004)</td>
<td>Solution: 200 units/ml Powder: 6,200 units/vial*</td>
<td>Purified ovine testicular hyaluronidase</td>
<td>*Note: The 6,200 unit was discontinued by the manufacturer (2009).</td>
</tr>
<tr>
<td>Wydase® by Wyeth-Ayerst (3/22/50)</td>
<td>Powder: 150 units/vial 1,500 units/vial Solution: 150 units/ml</td>
<td>Purified bovine testicular hyaluronidase</td>
<td>Note: Product was discontinued by the manufacturer (1/2001).</td>
</tr>
</tbody>
</table>


* Note: Hyaluronidase products are not USFDA-approved for the treatment of drug extravasation. This dose is for the adjuvant use to increase the dispersion and absorption of other injected drugs; hyaluronidase is added to the drug solution.
APPENDIX D2.
EVIDENCE FOR USE OF HYALURONIDASE WITH SPECIFIC AGENTS

Purpose: To summarize evidence for making recommendations for using hyaluronidase for IV extravasation of specific agents

Intended users: Nurses and licensed independent practitioners

Table D2. Summary of evidence supporting the efficacy of hyaluronidase with specific agents

<table>
<thead>
<tr>
<th>Extravasated Agent</th>
<th>Supporting Efficacy/ Evidence Grade</th>
<th>Supporting Inefficacy/ Evidence Grade</th>
<th>Recommendation Based on Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldesleukin</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>MacCara (1983) B</td>
<td>Micromedex (2010b) B</td>
<td>Consider hyaluronidase treatment</td>
</tr>
<tr>
<td>Asparaginase (Elspar®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Bleomycin (Blenoxane®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Calcium solutions</td>
<td>Laurie et al. (1984) A</td>
<td>Raszka et al. (1990) A</td>
<td>Treat with hyaluronidase</td>
</tr>
<tr>
<td></td>
<td>Micromedex (2010b) B</td>
<td>Montgomey et al. (1999) B</td>
<td></td>
</tr>
<tr>
<td>Carboplatin (Paraplatin®)</td>
<td></td>
<td></td>
<td>No evidence, other treatments available</td>
</tr>
<tr>
<td>Carmustine (BiCNU®)</td>
<td>Micromedex (2008a) B</td>
<td></td>
<td>Consider hyaluronidase treatment</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider hyaluronidase treatment</td>
</tr>
<tr>
<td></td>
<td>Micromedex (2010b) B</td>
<td>Cochran et al. (2002) C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Federle (1998) C</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence, other treatments available</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Dacarbazine (DTIC-Dome®)</td>
<td>Khan &amp; Holmes (2002) C</td>
<td></td>
<td>Weak evidence, other treatments available</td>
</tr>
</tbody>
</table>

1 1 hour delay
2 3, 6, 12 hour delay
3 May be less effective in children
Table D2. Summary of evidence (continued)

<table>
<thead>
<tr>
<th>Extravasated Agent</th>
<th>Supporting Efficacy/ Evidence Grade</th>
<th>Supporting Inefficacy/ Evidence Grade</th>
<th>Recommendation Based on Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dactinomycin (Cosmegen®)</td>
<td></td>
<td></td>
<td>No evidence, other treatments available</td>
</tr>
<tr>
<td>*Dobutamine</td>
<td></td>
<td>USFDA (2009) A</td>
<td>Contraindicated, other treatments available</td>
</tr>
<tr>
<td>*Dopamine</td>
<td></td>
<td>USFDA (2009) A</td>
<td>Contraindicated, other treatments available</td>
</tr>
<tr>
<td>*Epinephrine</td>
<td></td>
<td>USFDA (2009) A</td>
<td>Contraindicated; other treatments available</td>
</tr>
<tr>
<td>Epirubicin</td>
<td></td>
<td>Reeves (2007) B</td>
<td>Hyaluronidase not effective, other treatments available</td>
</tr>
<tr>
<td>Erythomycin</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider hyaluronidase treatment</td>
</tr>
<tr>
<td>Flucloxacillin (Floxacen®)</td>
<td>Khan &amp; Holmes (2002) C</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Fludarabine (Fludara®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Fluourouracil (Adrucil®)</td>
<td></td>
<td></td>
<td>No evidence, other treatments available</td>
</tr>
<tr>
<td>Gemcitabine (Gemzar®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Idarubicin (Idamycin®)</td>
<td>Reeves (2007) B</td>
<td></td>
<td>Hyaluronidase not effective, other treatments available</td>
</tr>
<tr>
<td>Ifosamide (Ifex®)</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence, other treatments available</td>
</tr>
<tr>
<td>Mannitol (≥15%)</td>
<td>Kumar &amp; Sprung (2003) D</td>
<td></td>
<td>Consider hyaluronidase treatment</td>
</tr>
</tbody>
</table>

* Use of hyaluronidase for this agent is contraindicated. Antidotes and other therapies are suggested.
### Table D2. Summary of evidence (continued)

<table>
<thead>
<tr>
<th>Extravasated Agent</th>
<th>Supporting Efficacy/ Evidence Grade</th>
<th>Supporting Inefficacy/ Evidence Grade</th>
<th>Recommendation Based on Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechlorethamine (Mustargen®)</td>
<td></td>
<td>Dorr (1990) B</td>
<td>Hyaluronidase not effective, other treatments available</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Khan &amp; Holmes (2002) C</td>
<td></td>
<td>Weak evidence</td>
</tr>
<tr>
<td>Mitomycin (Mutamycin®)</td>
<td></td>
<td>Dorr (1990) B</td>
<td>Hyaluronidase not effective, other treatments available</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td></td>
<td></td>
<td>No evidence, other treatments available</td>
</tr>
<tr>
<td><em>Norepinephrine</em></td>
<td></td>
<td>USFDA (2009) A</td>
<td>Contraindicated, other treatments available</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider hyaluronidase treatment</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Micromedex (2010b) B Montgomery et al. (1999) B</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>Potassium solutions</td>
<td>MacCara (1983) B Micromedex (2010b) B</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>Sodium tetradsyl sulfate</td>
<td>Zimmert (1993) A</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Stanley (2007) D</td>
<td></td>
<td>Weak evidence</td>
</tr>
</tbody>
</table>

* Use of hyaluronidase for this agent is contraindicated. Antidotes and other therapies are suggested.
* 4 At lower doses
* 5 At higher doses
### Table D2. Summary of evidence (continued)

<table>
<thead>
<tr>
<th>Extravasated Agent</th>
<th>Supporting Efficacy/ Evidence Grade</th>
<th>Supporting Inefficacy/ Evidence Grade</th>
<th>Recommendation Based on Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tromethamine</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Montgomery et al. (1999) B</td>
<td></td>
<td>Consider treatment with hyaluronidase</td>
</tr>
<tr>
<td>*Vasopressin</td>
<td></td>
<td></td>
<td>Contraindicated, other treatments available</td>
</tr>
</tbody>
</table>

* Use of hyaluronidase for this agent is contraindicated. Antidotes and other therapies are suggested.
### Table D2. Summary of evidence (continued)

<table>
<thead>
<tr>
<th>Extravasated Agent</th>
<th>Supporting Efficacy/ Evidence Grade</th>
<th>Supporting Inefficacy/ Evidence Grade</th>
<th>Recommendation Based on Literature</th>
</tr>
</thead>
</table>
APPENDIX D3.
DRESSINGS FOR IV EXTRAVASATION WOUNDS

**Purpose:** To compare dressings for IV extravasation wounds.

**Intended users:** Nurses and licensed independent practitioners

Table D3. Dressings for IV extravasation wounds*

<table>
<thead>
<tr>
<th>Dressing</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Hydrocolloids (DuoDerm®)  | • Promotes moist wound healing and autolytic debridement  
  • Can be left in place for 3-4 days | • May over hydrate wound and surrounding skin  
  • Excessive exudate** will leave the dressing sticky |
| Semipermeable (OpSite, Tegaderm™) | • Promotes moist wound healing  
  • Wound remains visible | • Does not absorb exudate*  
  • May injure intact skin on removal |
| Hydrofiber (Aquacel®)     | • Becomes gel when in contact with wound bed  
  • Highly absorptive and nonadherent | • May dehydrate wound due to absorptive nature |

* This is not an exhaustive list of all dressings available.
**A normal whitish exudate may form under these dressings as part of a normal autolytic debridement process. It is a normal process and should not be interpreted as an infection.

Evidence Grade = B: Clifton-Koeppel, 2006.
Permission was obtained through Mosby, Elsevier Health Sciences (http://www.us.elsevierhealth.com/).
APPENDIX D4.
TOPICAL TREATMENTS FOR IV EXTRAVASATION WOUNDS

**Purpose:** To compare topical treatments for IV extravasation wounds.

**Intended users:** Nurses and licensed independent practitioners

Table D4. Topical treatments for IV extravasation wounds*

<table>
<thead>
<tr>
<th>Topical</th>
<th>Uses</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacitracin</td>
<td>• Gram-positive organisms</td>
<td>• May promote Gram-negative bacterial growth</td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>• Gram-negative and gram-positive organisms</td>
<td>• Increased risk of kernicterus due to sulfur competing for with bilirubin for albumin binding sites, not recommended in infants &lt; 30 days old • Agranulocytosis • Cytotoxic to fibroblasts</td>
</tr>
<tr>
<td>Aquaphor®</td>
<td>• Superficial wounds to provide a moist wound environment</td>
<td>• Considered safe and preferred emollient</td>
</tr>
<tr>
<td>Amorphous hydrogels</td>
<td>• Treatment of sloughing or necrotic lesions • Facilitate auto debridement of wound by rehydrating slough and enabling enhanced rate of autolysis</td>
<td>• Unknown • Limited evidence from case reports</td>
</tr>
</tbody>
</table>

* This is not an exhaustive list of all topical treatments available.

Evidence Grade = B: Clifton-Koeppel, 2006; Montgomery et al., 1999.
Permission to use was obtained through Mosby, Elsevier Health Sciences (http://www.us.elsevierhealth.com/).
APPENDIX D5.

EXAMPLES OF QUICK REFERENCE CARDS

Purpose: To provide examples of rapidly access evidence-based information for what to do when an IV extravasation occurs.

Intended users: Nurses and licensed independent practitioners

Example D5a. Quick reference card for IV extravasations from University of Iowa Children’s Hospital

Example D5b. Quick reference card for hyaluronidase from University of Iowa Children’s Hospital

Copied with permission from: University of Iowa Hospital and Clinics, Children’s and Women’s Services (2011). Standard of Practice: N-CWS-PEDS-08.130.
QUICK REFERENCE CARD FOR IV INFILTRATIONS/EXTRAVASATIONS IN PEDIATRIC PATIENTS

DEFINITIONS

Extravasation/Infiltration – inadvertent administration of a solution or medication into a surrounding tissue, rated by a standard scale. For clinical purposes, the terms are used as synonyms, to include any agent.

Irritant - agents that have the potential to irritate tissue if extravasation occurs

Vesicant – a solution or medication that causes a blistering process

PATHOPHYSIOLOGY

Endothelial damage is caused when the cannula or needle tip dislodges or pierces the vein wall. This allows the infusate to block or constrict the vein or leak into the surrounding tissue. If the infusate continues to be delivered, there is a cycle of decreased cellular pH, loss of capillary wall integrity, phlebitis, edema, and eventually necrosis (potential effects depend on the agent that is extravasated).

Pain is generally the first sign or symptom of an infiltration/extravasation. However, not all infiltrates/extravasates are painful or show obvious signs of induration. Though initial swelling at the IV site is obvious, it may take 24 hours for darkening to appear in the skin. Damage is hard to evaluate because the skin is an unreliable indicator of the involvement of the subcutaneous fat and fascia. Absence of blistering does not give a foolproof indication of the extent of tissue damage either. Damage can continue for months after the initial insult. The unique mechanisms of the drugs action on the cells determine the specific pathophysiology and extent of an infiltrate/ extravasation.

RISK FACTORS

Patient Factors- preterm infants, neonates, children, ICU patients, co-morbidities (diabetes, circulation problems, obesity) or the inability to communicate pain.

Mechanical Factors- small, fragile, mobile or hard sclerosed veins, larger catheter size relative to vein size, IV site (areas of joint flexion, dominant hand), unstable catheter; uncontrolled patient activity or movement.

Physiological Factors- Clot formation above the cannulation site, thrombus or fibrin sheath at the catheter tip, impaired sensory perception, impaired circulation, lymphedema, superior vena cava syndrome or peripheral neuropathies.

Pharmacological Factors- hyperosmolar, ischemia inducing, alkaline or poorly water soluble agents and chemotherapies.

STAGING

A protocol for staging IV infiltrates/extravasations can be used to identify differences and generate interventions by licensed independent providers (LIPs) and nurses. An assessment of the IV site and quantitative staging should be documented by the nurse every hour and PRN. See Appendix A4b: Staging of IV Infiltrations.

Documentations of an infiltration/extravasation:

- Date and time of extravasation
- IV site location, catheter type, size and patency.
- Assessment of site and extremity including color and condition of the tissue, measurements of the area affected, if indicated.
- Patient symptoms and complaints.
- Medication and/or solution name, dose, route and dilution
- An estimate of the fluid volume.
- Stage of infiltration/extravasation per protocol.
- Interventions date and time.
- Notification of the LIP, consultations.
- Digital photographs are recommended. Scan to Electronic Medical record.

PREVENTION

Prevention of infiltration/extravasation includes:

- Recognizing vesicant/irritant properties of medications or solutions administered.
- Using preferred sites for administration; central line if possible or the dorsum of the hand and wrist.
- Educating nurses about infiltration and extravasation risks and interventions.
- Adequate dilution of medications.
- Avoiding the use of metal needles.
- Keeping the site visible by using a transparent dressing.
- Frequently assessing IV patency.
- Encouraging the patient to communicate any discomfort at the administration site.

INTERVENTIONS

The use of pharmacological and non-pharmacological treatments is somewhat discrepant in the literature. The use of hyaluronidase has been described for high osmotic solutions and other miscellaneous drugs. Phentolamine use is well described for some vasopressive drugs. Antidotal drugs for chemotherapeutic drugs are more variable and controversial. Elevation of the affected extremity is recommended for all infiltrates for at least 24 hours. Although the use of hot and cold is debated, it is generally agreed that moist heat should be avoided especially in the neonatal population. New surgical dressings and topicals are emerging to treat injuries related to infiltration/extravasation. Attempts should be made to aspirate offending infusate from the site through the infiltrated IV catheter. Prompt intervention is extremely important for mitigating damage. Treatment should be initiated as soon as possible and may be repeated depending on the extent of injury. What is most clear from the literature review is controlled experimental studies are lacking in pediatric populations (not feasible or ethical to do studies). Generalizations to the pediatric population are very limited and should be given careful consideration on an individual basis.

***See Appendix A5b: Clinical Algorithm for IV Extravasations
Evidence of extravasation may include:
- INSTANT:
  - Administration, dose administered and adjuvant therapies.
  - Volume, characteristics of the patient, timeliness of and clinical reports support use for this purpose.
- Delayed:
  - Extravasations, although randomized clinical trials in animal models, retrospective and descriptive studies in humans, and clinical reports support use for this purpose. Efficacy of models, retrospective and descriptive studies in humans, and clinical reports support use for this purpose.
- Long-term:
  - Stage 2 or greater extravasation
  - Any amount of vesicant drug
  - Some irritants, depending on concentration
  - Any amount of blood products
  - Agent specific recommendations.

**PATHOPHYSIOLOGY**

Five mechanisms may activate tissue necrosis when an extravasation occurs: 1) direct cellular toxicity, 2) osmotic disturbances across the cell membrane leading to cell death, 3) ischemic necrosis, 4) mechanical compression, and 5) bacterial colonization. Consequences range from a short term inflammatory response to severe necrosis requiring surgical intervention and may cause long term disabilities. The extent of damage caused by vesicant/irritant extravasation depends on the agent administered, amount extravasated, anatomical location, and the treatment administered.

**PHARMACOLOGY**

Hyaluronidase is an enzyme spreading agent that can be used to treat IV extravasations. Action of the enzyme temporarily breaks down hyaluronic acid, which is a major component of the normal interstitial barrier of connective tissue and allows for dispersion and absorption of the offending agent over a larger surface area. Within 24 to 48 hours the connective tissue barrier is regenerated.

**SAFETY AND EFFICACY**

Hyaluronidase for injection has been marketed for over 50 years. The efficacy of hyaluronidase to increase absorption and dispersion of other drugs products is supported by the FDA. It is not FDA-approved for the treatment of extravasations, although randomized clinical trials in animal models, retrospective and descriptive studies in humans, and clinical reports support use for this purpose. Efficacy of treatment depends on the extravasated drug properties and volume, characteristics of the patient, timeliness of administration, dose administered and adjuvant therapies.

**ASSESSMENT**

Evidence of extravasation may include:
- Loss of blood return
- Leakage at the site
- Change in infusion flow, occlusion alarms
- Pain or burning at the site.
- Cool skin at the site
- Erythema, blanching, or mottling of the skin
- Edema
- Blistering
- Darkening of the skin
- Inflammation*
- Induration*
- Ulceration*
- Sloughing*
- *Occurs later

Get help: FAST! Administer hyaluronidase as soon as possible after the event.

Timely administration is a key factor in achieving positive results. There are no clear rules as to how long after an extravasation occurs that treatment may be beneficial. Delays of > 1 hour may be less effective.

Activate Other Resources:
- CWS Standard of Practice on the Point.
- Pharmacy
- Page Nursing supervisor
- Contact LIP, attending staff as needed
- Consults: surgery, burn treatment team, wound care specialist, physical therapy as indicated

**INDICATIONS FOR TREATMENT**

- Stage 2 or greater extravasation
- Any amount of vesicant drug
- Some irritants, depending on concentration
- Any amount of blood products
- Agent specific recommendations.

**ADMINISTRATION**

1. Immediately stop the infusion but DO NOT remove cannula
2. Evacuate the extravasate. Try to evacuate the extravasate through the original catheter if it is still in place by aspirating residual drug using a 1-10 ml syringe.
3. Determine if hyaluronidase is indicated for treatment. See Table D2b.
4. Discontinue peripheral IV if hyaluronidase is indicated for treatment. Avoid excess pressure at the site. Do not use the extremity for subsequent IVs.
5. Follow manufactures recommendations for administration.
- Dosage: Most typically for absorption and dispersion of drugs, 15 or 150 units/ml hyaluronidase is injected. A typical dose for neonates and smaller infiltrations is 15 units/ml. Higher doses (150 unit/ml) may be indicated for vesicant chemotherapies or large extravasations in non-infants.
- Route: Hyaluronidase may be given subcutaneous or intradermal, IV administration should be avoided.
- Reconstitution: Hyaluronidase is typically reconstituted by pharmacy with normal saline and diluted to make a solution of the desired concentration in 1 ml.
- Administration: Hyaluronidase in 5 injections (0.2 ml per injection for total 1 ml) around the circumference of the affected area, intradermal (ID) or SQ, using a new 30 gauge needle for each injection.
6. Consider repeating as needed There are no clear guidelines for how often or when hyaluronidase can be repeated.
7. Assess and manage pain Pain due to the extravasation should be managed with supportive interventions. Mild pain may require systemic analgesics and non-pharmacologic comfort measures. Moderate to severe pain may require oral or IV opioids.

**WARNINGS**

Do NOT use hyaluronidase with vasoconstrictive drugs such as dopamine.
Do NOT use in areas of infection, tumors or acute inflammation.
NOT for IV administration
QUICK REFERENCE CARD
HYALURONIDASE USE FOR IV INFILTRATIONS/EXTRAVASATIONS IN PEDIATRIC PATIENTS

AGENT SPECIFIC RECOMMENDATIONS FOR TREATMENT WITH HYALURONIDASE:

<table>
<thead>
<tr>
<th>Treat</th>
<th>Consider Treatment</th>
<th>Explore other treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of hyaluronidase for this agent is supported by efficacy in two or more sources.</td>
<td>Efficacy of hyaluronidase for this agent is supported but evidence is limited, consider treatment.*</td>
<td>Use of hyaluronidase is contraindicated for these agents and/or other effective antidotes are available for treatment.**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calcium solutions</th>
<th>Aminophylline</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast media</td>
<td>Carmustine</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Dextrose solutions (≥ 10%)</td>
<td>Chloramphenicol</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Erythromycin</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Hypertonic saline ≥ 3%</td>
<td>Dactinomycin</td>
</tr>
<tr>
<td>Etoposide phosphate</td>
<td>Mannitol (≥ 15% concentration)</td>
<td>Daunorubicin</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Oxacillin</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Penicillin</td>
<td>Dofetilide</td>
</tr>
<tr>
<td>Total Parenteral Nutrition</td>
<td>Phenytoin</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Potassium solutions</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Sodium tetradecyl sulfate</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Teniposide</td>
<td>Idarubicin</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Tromethamine</td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Mitomycin</td>
</tr>
</tbody>
</table>

* Consider hyaluronidase for treatment of any large volume extravasation (EXCEPT when other treatments available, clear evidence of inefficacy, or contraindicated**).

ADJUVANT THERAPIES: Other therapies that may enhance the effectiveness of hyaluronidase.

**Positioning**: Elevate the affected site for 24 to 72 hours to decrease edema and aid in normal absorption of extravasated fluids.

**Thermal modalities**: With the exception of vinca alkaloids, there is no clear evidence regarding the benefit of thermal modalities with hyaluronidase.

**Saline flushout**: Saline flushout is a technique that physically removes any extravasated material from the tissue. It may be indicated when there are multiple agents extravasated or for extravasations of large volumes or vesicant agents. Techniques for saline washout vary from multiple injections or stab wounds, with or without irrigation and manual squeezing, to surgical incisions, fluorescence microscopy, irrigation, and liposuction.

**Medications**: When considering administration of other drugs with hyaluronidase, it is recommended to consult references for precautions with the other drug.

**Dressings and topicals**: Promotion of a moist wound environment using various topical medications and dressings reduces healing time, decreases incidence of infection and prevents undue scarring.

**Surgical consultation and intervention**: Surgical treatment is indicated for large volume extravasations, deep extravasation through a central line, severe pain up to two weeks after the injury, or if treatment with hyaluronidase fails to prevent progression of the extravasation.

**Fluorescence Microscopy**: Intraoperative fluorescence injections can be used to demarcate viable tissue and locate deposits of medications such as anthracyclines and guide surgical excision of necrotic tissues.
Example D5c. Quick reference card for IV extravasations from North Trent Cancer Network-Extravasation Guidelines

9.0 QUICK GUIDE FOR IMMEDIATE TREATMENT OF EXTRAVASATION VIA A PERIPHERAL CANNULA

Extravasation suspected – stop drug administration, assess the extent of extravasation, the drug involved and any help needed.

Wearing goggles, withdraw through the cannula, removing as much of the drug as possible.

Remove the cannula and mark around the extravasated area, using a pen. Consider the patients need for analgesia.

Inform the doctor. Treat according to the guidelines for the management of extravasation. Treatment to be prescribed by the doctor or carried out by an extravasation nurse practitioner working within a patient group direction.

Document the incident and care given in the patient records.

If there appears to be any visible signs of extravasation, take a photograph and file in the medical notes.

Ensure the appropriate follow up arrangements are in place including giving the patient the appropriate colour coded information leaflet for the drug involved.

Complete local incident form and North Trent extravasation reporting form. Ensure copies are sent to appropriate personnel according to local policy. Attach photograph where appropriate.

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Hyaluronidase for Treatment of Intravenous Extravasations Evidence-Based Guideline
©The University of Iowa College of Nursing
Written 2012
APPENDIX D6.
EXAMPLES OF PATIENT INFORMATION SHEETS FOR MANAGING EXTRAVASATIONS

**Purpose:** To provide examples of evidence-based patient information for what to do when an IV extravasation occurs.

**Intended users:** Nurses and licensed independent practitioners, patients and families.

**Example D6. Patient information for managing extravasations**

**Patient Information Sheet – managing extravasation**

*Front page of all extravasations*

**What is extravasation?**
Chemotherapy is often given as fluid into a vein through a thin hollow tube called a cannula. Occasionally a cannula can become dislodged or blocked causing the chemotherapy to go into the skin area around the vein. When this happens this is called extravasation.

**What can happen as a result?**
The effect of extravasation depends on a number of factors. These include:
- The type of chemotherapy drug that was being given
- The amount of chemotherapy that went into the area around the vein

Some chemotherapy can cause irritation, pain and tissue damage that is temporary. This usually responds to simple treatments and will get better over a few weeks. Other chemotherapy can lead to a more severe reaction and can cause blistering and more permanent damage. This damage may not appear until a few days, or weeks later. Your nurse, or doctor, will tell you which of these types of chemotherapy you have been given.

**How will the extravasation be treated?**
The treatment you receive will depend on the chemotherapy you were given and the amount of drug that went in to the tissue. The treatment you will receive is described on the back of this leaflet.

**What should I do?**
Please continue with the treatment your doctor or nurse has advised you to carry out. Have a look at the area regularly, at least twice a day, and let us know if you have any concerns or notice any of the following:
- There are changes in the affected area (for example, it seems redder, the affected area is getting bigger, you notice fluid leaking from the skin)
- The area feels more painful
- There have been no improvements after 3 days

**Who should I contact if I have any concerns?**
If you have any concerns you should contact the area where you had your treatment during the times that the treatment area is open. You will have been given the contact details by your treatment area.

Outside these times contact the nursing bleep holder at Weston Park Hospital through the hospital switchboard: 0114 226 5000.
Group C - Red

Management of extravasation

Your extravasation has happened with a type of chemotherapy that can cause long term damage. However, this may be reduced by careful management of the problem.

When your extravasation happened the doctor, or nurse, may have given you some small injections into the area around the vein. These were injections of a drug that helped remove the chemotherapy from the area around the vein. After this a warm pad may have been put on for one hour.

You are now advised to elevate (raise) the arm that was involved in the extravasation. This can be done by resting your arm on 2 or 3 pillows or cushions when sitting or lying down. This should be done as much as possible for 2 days – but you should still use and move your arm. After 2 days you should use your arm as usual.

It is very important for you to have a look at the skin where the extravasation occurred a few times a day and let us know if you notice any problems. You will be asked to return to the hospital within the next 2 to 3 days so that the area can be examined.

You have an appointment to return to: ______________________ (ward/dept)

Date: ______________________

Time: ______________________

To be given to patients who have received drugs from group C

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APPENDIX E
EVIDENCE-BASED STANDARDS

Appendix E contains examples of evidence-based standards that may be useful for developing institution-specific policies and procedures using the *Hyaluronidase for Treatment of IV Extravasations Guideline*:

- E1. Examples of IV extravasation procedures
- E2. Example IV extravasation wound care protocol
APPENDIX E1.
EXAMPLE OF IV EXTRAVASATION PROCEDURES

**Purpose:** To provide examples of IV extravasation procedures developed by an institution using this guideline.

**Intended users:** Nurses, licensed independent practitioners, and pharmacist.

Example E1. IV extravasation procedures from the University of Iowa Children’s Hospital IV therapy standard of practice.

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**Example E1. IV extravasation procedures from the University of Iowa Children’s Hospital IV therapy standard of practice.**

**Policy and Procedure Manual**

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**Children’s and Women’s Services Standard of Practice**

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**N-CWS-PEDS-08.130**

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**PROCEDURE:**

*IV Infiltration/Extravasation Interventions*

(See Infiltration/Extravasations in Pediatric Patients Quick Reference)

1. Assess the site for evidence of Infiltration/Extravasation. Though initial swelling at the IV site is obvious, it may take 24 hours for darkening to appear in the skin. Therefore, tissue damage is hard to evaluate in the immediate period. \(R_2\)
   
a. Consider marking the site with a pen in order to track progression

2. Identify stage of infiltration/extravasation and the recommended interventions using Staging of IV Infiltrations/Extravasations (Table 3) and the Decision Algorithm for IV Extravasations (Figure 1). \(R_1\)
   
a. Stage 0 – No intervention will be needed.
   
b. Stage 1 – A rating at this level will indicate the nurse should:
      1) Check tape/IV securement
      2) Elevate extremity
      3) Consider using alternative site for medications and IV fluids
   
c. Stage 2 – A rating at this level will indicate that the nurse should:
      1) Stop the infusion.
2) At nursing discretion may: *Get help, FAST* by notifying LIP and activating other resources. Timely administration of treatments/antidotes after an extravasation is a key factor in achieving positive results.

3) Attempt to aspirate back any residual fluid from the existing catheter.

4) Remove IV if not needed for treatment/antidote administration.

5) Elevate extremity.

6) Treatment: At LIP discretion, may opt to treat in some cases.

7) If IV is still in place, remove it. $R_2$

d. Stage 3 and 4 – A rating at this level will indicate that the nurse should:

1) Stop the infusion

2) Anticipate treatment: *Get help, FAST* by notifying LIP and activating other resources. Timely administration of treatments/antidotes after an extravasation is a key factor in achieving positive results.

3) Attempt to aspirate back any residual fluid from the existing catheter.

4) Remove IV if not needed for treatment/antidote administration.

5) Elevate the extremity.

6) Treatment: At LIP discretion.

7) If IV is still in place, remove it. $R_2$

3. Carry out treatment as ordered by LIP. See Table 4: *Treatments for Extravasation by Drug Name* for specific treatment specific recommendations. $R_2$

a. Administer according to treatment specific procedures and package insert. See treatment specific procedures to follow.

b. Remove peripheral IV catheter after treatment or when determined that it is not needed for treatment. See treatment specific procedures to follow. $R_2$

c. Avoid applying pressure at the site.

d. Apply thermal modalities if indicated. See Department of Nursing Services and Patient Care Standard of Practice, *Low Heat and Cold Application, Thermal Modalities [N-02.081]*. See Table 4: *Treatments for Extravasation by Drug Name* for specific recommendations. General principles related to IV extravasations are as follows:

1) Apply cold to site to localize the infiltrate (for 20 minutes, 4 times daily for 1-2 days). Cold is recommended for anthracyclines (e.g., doxorubicin, daunorubicin) extravasations. In general, topical cooling appears to be a preferred choice after extravasations.

2) Apply heat to site, if desired, to dispense the infiltrate into surrounding tissue (for 20 minutes, 4 times daily for 1-2 days). Heat is recommended for vinca alkaloids (e.g., vincristine, vinblastine, vinorelbine) extravasations. Avoid heat with anthracyclines.

3) Application of heat therapy may not be applicable for premature or newborn infants. Application of heat and cold therapy may not be warranted for patients with neurological limb impairments or inability to
self-report. Moist heat should be avoided, especially in the neonatal population. R1

e. Consult other services as needed for further treatment

1) Pharmacy
2) Wound care specialist (dressings)
3) Burn treatment team
4) Surgeons (if considering saline washout, or for large volume extravasations, compartment syndrome, severe pain up to two weeks after the injury, or if treatment fails to prevent progression of the extravasation injury)
5) Physical therapy

f. Manage patient pain and comfort needs (pain scale scores, pharmacologic and nonpharmacologic interventions). Mild pain due to extravasation may require systemic analgesics and non-pharmacologic comfort measures. Moderate to severe pain may require oral or IV opioids. R2

4. Document infiltration/extravasation and treatment if greater than stage 2, if antidote given or at nurse discretion.

a. Assessment and documentation of site and response will be done every hour x 6 hours, every 4 hours x 24 hours, and then PRN.

1) After extravasation, initial assessments often are unreliable in predicting the ultimate degree of tissue involvement and damage.
2) Digital photographs are recommended. Scan to electronic medical record media. L4


5. Educate patient/family (e.g., skin assessment, reporting pain and other symptoms).

PROCEDURE:

_Hyaluronidase Administration_

(See [Hyaluronidase for IV Extravasations in Pediatric Patients Quick Reference](#))

1. Determine if hyaluronidase treatment of the IV extravasation is indicated using Table 4: Treatments for Extravasation by Drug Name for specific recommendations and other agent specific resources. R2 R6

2. After aspirating back residual infiltrated agent, remove the IV catheter. R2

3. As per EPIC order set: PEDNICU: IV INFILTRATE for the NICU only and PED: IV INFILTRATE for non NICU, pharmacy will prepare and deliver hyaluronidase solution of 15 or 150 units per ml. A typical dose for neonates or smaller infiltrations is 15 units/ml. Higher doses (150 unit/ml) may be indicated for vesicant chemotherapies or large extravasations in non-infant patients. LIP to determine dose. R2
a. Note Vitrase™ (hyaluronidase) comes as a 200 unit/ml solution and needs dilution by pharmacy to achieve desired concentration.

b. Timely administration is important, this medication should always be ordered STAT. Hyaluronidase is most effective if given within one hour of the event and possibly effective for 24 hours or more after an event. However, there are no clear rules as to how long after an event hyaluronidase may be beneficial. R₂

4. Administer hyaluronidase in 5 injections of 0.2 ml per injection (1 ml total) around the circumference of the affected area, intradermal (ID) or subcutaneous (SQ), using a new 30 gauge needle for each injection. R₂

a. Hyaluronidase is NOT for IV administration.

b. Hyaluronidase should NOT be used to treat vasoconstrictive agents (such as dopamine, dobutamine, epinephrine or norepinephrine).

c. Hyaluronidase may be repeated with large extravasations, vesicant chemotherapies or continued progression of the injury. There are no clear guidelines as to when. The onset of action is immediate, with a 24-48 hour duration of effect.
### TREATMENTS FOR EXTRAVASATION BY DRUG NAME

<table>
<thead>
<tr>
<th>Drug</th>
<th>Extravasation potential</th>
<th>Treatments (Preferred in bold)</th>
<th>Thermal Modalities</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>None</td>
<td>None</td>
<td>Apply cold</td>
<td></td>
</tr>
<tr>
<td>Aldesleukin</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>Hyaluronidase***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic Trioxide (Trisenox®)</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asparaginase (Elisparsat®)</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleomycin (Blenoxane®)</td>
<td>None or irritant</td>
<td>None</td>
<td>Apply cold</td>
<td></td>
</tr>
<tr>
<td>Calcium solutions</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin (Paraplatin®)</td>
<td>None or irritant if ≥ 10 mg/ml concentration</td>
<td>None or Dimethyl sulfoxide or Sodium thiosulfate</td>
<td>Apply cold †</td>
<td></td>
</tr>
<tr>
<td>Carmustine (BiCNU®)</td>
<td>Irritant or vesicant</td>
<td>Hyaluronidase or Sodium thiosulfate or None</td>
<td>Apply cold †</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol (Non-Formulary, NF)</td>
<td>Unknown</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Cisplatin (Platinol®)         | Irritant or vesicant (≥0.5 mg/ml) | None or Sodium thiosulfate or Dimethyl sulfoxide | Apply cold † | If extravasate ≥ 20 ml and ≥ 0.5 mg/ml concentration then ORDER: 2 ml of 1/6M (40 mg/ml) Na thiosulfate for each 100 mg Cisplatin †

If extravasate < 20 ml or < 0.5 mg/ml concentration it is considered an irritant and no treatment is indicated.

Doses for newborns and infants are not established.

Cladribine (Leustatin®)         | None                    | None                           |                   |             |
| Clofarabine (Clolar®) (NF)     | None                    | None                           |                   |             |
| Contrast media                | Hyperosmolar solution   | Hyaluronidase**                |                   |             |
| Cyclophosphamide (Cytoxan®)   | None or irritant        | None or Sodium thiosulfate     | Apply cold        |             |
| Cytarabine (Cytosar®)         | None                    | None                           |                   |             |
| Dacarbazine (DTIC-Dome®)      | Irritant or vesicant    | None or Dimethyl sulfoxide or Sodium thiosulfate | Apply cold † | Na thiosulfate is recommended only when high concentrations of dacarbazine extravasates. §

†Consider Hyaluronidase for treatment of any large volume extravasation (unless other treatments available, clear evidence of inefficacy, or contraindicated).

† Conservative treatment including applying cold and elevation recommended (Cadence Pharmaceutical).

*Efficacy of Hyaluronidase for this agent is supported, but evidence is limited (Hanrahan, in press).

**Research and other evidence supports the use of hyaluronidase with this agent (Hanrahan, in press).

***Efficacy of Hyaluronidase for this agent is supported by expert opinion (Tierney, 2011).

† Supported treatment according to Children’s Oncology Group Extravasation Guidelines (2007).

§ Supported treatment according to DRUGDEX® System: Thomson Reuters (Healthcare) Inc. (2010).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Extravasation potential</th>
<th>Treatments(\text{Preferred in bold})</th>
<th>Thermal Modalities</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dactinomycin (Cosmegen(^8))</td>
<td>Vesicant DNA binding</td>
<td>None(^\ast) or Dimethyl sulfoxide(^\ast)</td>
<td>Apply cold</td>
<td>Avoid heat and direct sunlight</td>
</tr>
<tr>
<td>Daunorubicin (Cerubidine(^8))</td>
<td>Vesicant DNA binding</td>
<td>Dexrazoxane(^1) or Dimethyl sulfoxide(^1)</td>
<td>Apply cold</td>
<td>(remove cooling packs at least 15 minutes prior to dexrazoxane infusion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Avoid heat and direct sunlight</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Corticosteroids are CONTRAINDICATED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyaluronidase is NOT effective with this agent.</td>
</tr>
<tr>
<td>Dextrose solutions (≥ 10%)</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Ischemia-inducing agent</td>
<td>None or Phentolamine is an option, but not generally needed</td>
<td></td>
<td>Hyaluronidase is CONTRAINDICATED</td>
</tr>
<tr>
<td>Docetaxel (Taxotere(^9))</td>
<td>Vescant or irritant</td>
<td>None(^\ast) or Hyaluronidase**</td>
<td>Apply cold</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Ischemia-inducing agent</td>
<td>Phentolamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Vesicant DNA binding</td>
<td>Dexrazoxane(^1) or Dimethyl sulfoxide(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Adriamycin(^8))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOT to be used together as combination may increase tissue damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Corticosteroids and hyaluronidase are CONTRAINDICATED</td>
</tr>
<tr>
<td>Doxorubicin, Liposomal (Doxil(^8))</td>
<td>Irritant</td>
<td>None</td>
<td>Apply cold</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Ischemia-inducing agent</td>
<td>None or Phentolamine is an option, but not generally needed</td>
<td></td>
<td>Hyaluronidase is CONTRAINDICATED</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Vescant</td>
<td>Dexrazoxane(^1) or Dimethyl sulfoxide(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide (VePesid(^7))</td>
<td>Irritant or Vesicant</td>
<td>Hyaluronidase**</td>
<td>Apply warm</td>
<td>Only need hyaluronidase treatment for large volumes or concentrated solutions</td>
</tr>
<tr>
<td>Etoposide phosphate (Etopophos(^8)) NF</td>
<td>Irritant</td>
<td>Hyaluronidase(^\ast)</td>
<td>Apply warm</td>
<td></td>
</tr>
<tr>
<td>Fludarabine (Fludara(^8))</td>
<td>None</td>
<td>None(^\ast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil (Adrucil(^7))</td>
<td>Irritant or none</td>
<td>None(^\ast) or Dimethyl sulfoxide(^\ast)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\text{Consider Hyaluronidase for treatment of any large volume extravasation (unless other treatments available, clear evidence of inefficacy, or contraindicated).}\)

\(^*\)Efficacy of Hyaluronidase for this agent is supported, but evidence is limited (Hanrahan, 2010).

\(^**\)Research and other evidence supports the use of hyaluronidase with this agent (Hanrahan, 2010).

\(^***\)Efficacy of Hyaluronidase for this agent is supported by expert opinion (Tierney, 2011).

\(^\dagger\)Supported treatment according to Children’s Oncology Group Extravasation Guidelines (2007).

\(^\S\)Supported treatment according to DRUGDEX\(^8\) System: Thomson Reuters (Healthcare) Inc. (2010).
### TREATMENTS FOR EXTRAVASATION BY DRUG NAME (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Extravasation potential</th>
<th>Treatments(^a) (Preferred in <strong>bold</strong>)</th>
<th>Thermal Modalities</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine (Gemzar(^a))</td>
<td>None or irritant</td>
<td>None(^b)</td>
<td>None(^c)</td>
<td></td>
</tr>
<tr>
<td>Gemtuzumab (Mylotarg(^a))</td>
<td>Irritant</td>
<td><strong>Hyaluronidase</strong></td>
<td>Apply cold(^d)</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Hyperosmolar solution</td>
<td><strong>Hyaluronidase</strong></td>
<td>Hyaluronidase(^e)</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline (≥ 3% NaCl)</td>
<td>Hyperosmolar solution</td>
<td><strong>Hyaluronidase</strong></td>
<td>Hyaluronidase(^e)</td>
<td></td>
</tr>
<tr>
<td>Idarubicin (Idamycin(^b))</td>
<td>Viscant DNA binding</td>
<td><strong>Dexrazoxane</strong> or Dimethyl sulfoxide(^c)</td>
<td>Apply cold(^d)</td>
<td>Do not use extremity for 48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>NOT to be used together as combination may increase tissue damage</strong></td>
<td></td>
<td>Corticosteroids are CONTRAINDIATED</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Hyaluronidase is NOT effective with this agent.</strong></td>
</tr>
<tr>
<td>Ifosfamide (Ifex(^b))</td>
<td>Irritant</td>
<td>None(^c) or Dimethyl sulfoxide(^c)</td>
<td>Apply cold(^d)</td>
<td>Do NOT apply heat, it may increase cytotoxicity(^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan (Camptosar(^b))</td>
<td>Viscant DNA binding</td>
<td><strong>Apply cold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol (≥15%)</td>
<td>Hyperosmolar solution</td>
<td><strong>Hyaluronidase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechlorethamine (Mustargen(^b))</td>
<td>Viscant DNA binding</td>
<td>Sodium thiosulfate(^c)</td>
<td>None(^c)</td>
<td><strong>Timely (STAT) administration is crucial with this agent</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ml of 1/6M (40 mg/ml) sodium thiosulfate for each 1 mg of mechlorethamine extravasated(^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>REPEAT doses over next several hours</strong>(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Hyaluronidase is NOT effective with this agent.</strong></td>
</tr>
<tr>
<td>Melphalan (Alkeran(^b))</td>
<td>Irritant or vesicant</td>
<td>None(^c)</td>
<td>Cold(^d)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>None</td>
<td>None(^c)</td>
<td>None(^c)</td>
<td></td>
</tr>
<tr>
<td>Mitomycin (Mutamycin(^b))</td>
<td>Viscant</td>
<td><strong>Dimethyl sulfoxide</strong> or Sodium thiosulfate(^c) or Pyridoxine(^c)</td>
<td>None(^c) or cold(^c)</td>
<td>Delayed injuries have been documented at sites distant from the extravasation(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyridoxine (vitamin B(_6)) may slow or prevent necrosis with this agent. Dilute (1-3 fold) and administer 75-300 mg SQ at site.(^d)</td>
<td>Avoid heat and direct sunlight(^c)</td>
<td><strong>Hyaluronidase is NOT effective with this agent.</strong></td>
</tr>
</tbody>
</table>

\(^a\)Consider Hyaluronidase for treatment of any large volume extravasation (unless other treatments available, clear evidence of inefficacy, or contraindicated).

\(^b\)Efficacy of Hyaluronidase for this agent is supported, but evidence is limited (Hanrahan, 2010).

\(^c\)Research and other evidence supports the use of hyaluronidase with this agent (Hanrahan, 2010).

\(^d\)Efficacy of Hyaluronidase for this agent is supported by expert opinion (Tierney, 2011).

\(^e\)Supported treatment according to Children’s Oncology Group Extravasation Guidelines (2007).

\(^f\)Supported treatment according to DRUGDEX\(^k\) System: Thomson Reuters (Healthcare) Inc. (2007, 2008).
## TREATMENTS FOR EXTRAVASATION BY DRUG NAME (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Extravasation potential</th>
<th>Treatmentsa (Preferred in bold)</th>
<th>Thermal Modalities</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoxantrone (Novantrone®)</td>
<td>Irritant or vesicant (rare) DNA binding</td>
<td><strong>Dexrazoxane</strong> or Dimethyl sulfoxide†</td>
<td>Apply cold (remove cooling packs at least 15 minutes prior to dexrazoxane infusion)</td>
<td></td>
</tr>
<tr>
<td>Nafcinllin</td>
<td>Irritant</td>
<td>Hyaluronidase**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelarabine (Arranon®) (NF)</td>
<td>None</td>
<td>None†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Ischemia-inducing agent</td>
<td>Phenolamine</td>
<td>Hyaluronidase is CONTRAINDIATED</td>
<td></td>
</tr>
<tr>
<td>Oxacillin (NF)</td>
<td>Irritant</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin (Eloxatin®)</td>
<td>Vescant or irritant Non-DNA binding</td>
<td>None or Sodium thiosulfate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (Taxol®)</td>
<td>Vescant or irritant Non-DNA binding</td>
<td>Hyaluronidase**† Cold†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegasparase (Oncaspar®)</td>
<td>None</td>
<td>None†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Irritant</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Poorly water soluble agent, alkaline</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium solutions</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium tetradecyl sulfate</td>
<td>Sclerosis agent</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teniposide (Vumon®) (NF)</td>
<td>Irritant or vesicant</td>
<td>Hyaluronidase**†</td>
<td>Apply cold or warm†</td>
<td>Treatment with hyaluronidase is only indicated for large volume or highly concentrated extravasations of this agent.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiotepa (Thioplex®)</td>
<td>None</td>
<td>None†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topotecan (Hycamtin®)</td>
<td>Irritant</td>
<td>Hyaluronidase*</td>
<td>Apply cold†</td>
<td></td>
</tr>
<tr>
<td>Total Parenteral Nutrition</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tromethamine</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Hyperosmolar solution</td>
<td>Hyaluronidase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Ischemia-inducing agent</td>
<td>Phenolamine†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Consider Hyaluronidase for treatment of any large volume extravasation (unless other treatments available, clear evidence of inefficacy, or contraindicated).

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**Research and other evidence supports the use of hyaluronidase with this agent (Hanrahan, 2010).

***Efficacy of Hyaluronidase for this agent is supported by expert opinion (Tierney, 2011).

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§ Supported treatment according to DRUGDEX® System: Thomson Reuters (Healthcare) Inc. (2007; 2008).
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<table>
<thead>
<tr>
<th>Drug</th>
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<th>Treatments‡ (Preferred in <strong>bold</strong>)</th>
<th>Thermal Modalities</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinblastine sulfate (Velban®)</td>
<td>Vesicant Non-DNA binding</td>
<td>Hyaluronidase**†</td>
<td>Apply warm**†</td>
<td>Cold is CONTRAINDIQUED</td>
</tr>
<tr>
<td>Vincristine sulfate (Oncovin®)</td>
<td>Vesicant Non-DNA binding</td>
<td>Hyaluronidase**†</td>
<td>Apply warm**†</td>
<td>Cold is CONTRAINDIQUED</td>
</tr>
<tr>
<td>Vinorelbine (Navelbine®)</td>
<td>Vesicant Non-DNA binding</td>
<td>Hyaluronidase**†</td>
<td>Apply warm**†</td>
<td>Cold is CONTRAINDIQUED</td>
</tr>
</tbody>
</table>

‡Consider Hyaluronidase for treatment of any large volume extravasation (unless other treatments available, clear evidence of ineffectivity, or contraindicated).
*Efficacy of Hyaluronidase for this agent is supported, but evidence is limited (Hanrahan, 2010).
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§ Supported treatment according to DRUGDEX® System: Thomson Reuters (Healthcare) Inc. (2007; 2008).
REFERENCES


LITERATURE REFERENCES:


RESEARCH REFERENCES:


R2 Hanrahan, K. (In press). Hyaluronidase for IV Extravasation Evidence-Based Guideline. The University of Iowa College of Nursing Gerontological Nursing Interventions Research Center, Research Translation and Dissemination Core.


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Posted: 7/10
APPENDIX E2.
EXAMPLE OF IV EXTRAVASATION WOUND CARE PROTOCOL

**Purpose:** To provide an example of an evidence-based IV extravasation wound care protocol.

**Intended users:** Nurses and licensed independent practitioners

Example E2. Intravenous extravasation staging and suggested wound care protocol from University Children’s Hospital at UCI Medical Center
Hyaluronidase for Treatment of Intravenous Extravasations

---

**IV INFILTRATION WOUND CARE**

**Stage I-II**
- Generally only supportive care required
- Elevation of site
- Aquaphor® to any skin damage

**Stage III-IV**
- Hyaluronidase (Vitrase® or Amphadase®) injection
- Following saline washout, apply Aquaphor® to damaged area and cover with 2x22
- 24 hours later, apply DuoDerm® to injury
- Change dressing daily
- Rinse with normal saline at

**Stage V**
- Hyaluronidase (Vitrase® or Amphadase®) injection
- Vigilon® dressing, Aquaphor wrap with saran wrap
- Change dressing daily
- Rinse with normal saline at dressing change

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| I     | Painful IV site  
        | No erythema 
        | No swelling |
| II    | Painful IV site 
        | Slight swelling (0-20%) 
        | No blanching 
        | Good pulses below the infiltration site |
| III   | Painful IV site 
        | Marked swelling (30-50%) 
        | Blanching 
        | Skin cool to touch 
        | Good pulses below the infiltration site |
| IV    | Painful IV site 
        | Very marked swelling (>50%) 
        | Blanching 
        | Decreased or absent pulses* 
        | Capillary refill > 4 seconds* |
| V     | Any or all of Stage IV characteristics AND 
        | Extensive wounding, involving most of the extremity |
        | Hyaluronidase (Vitrase® or Amphadase®) injection |
        | Vigilon® dressing, Aquaphor wrap with saran wrap |
        | Change dressing daily |
        | Rinse with normal saline at dressing change |
        | Deep wounding |

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REFERENCES

Key: (R) = Research (L) = Non-research Literature (N) = National Guidelines
* Sources not meeting inclusion criteria but supplementing guideline content.


COG Pharmacy Committee & COG Nursing Clinical Practice Committee: Acute/Palliative Care Section. (2007). Extravasation guidelines. Children’s Oncology Group unpublished guidelines. (R)


Hyaluronidase for Treatment of Intravenous Extravasations

Hyaluronidase for Treatment of Intravenous Extravasations

Evidence-Based Guideline

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Written 2012


University of Iowa Hospital and Clinics, Children’s and Women’s Services, (2011). Standard of Practice: N-CWS-PEDS-08.130.*

U. S. Department of Health and Human Services, Food and Drug Administration. (November 6, 2003). Determination that hyaluronidase for injection was not withdrawn from sale for reasons of safety or effectiveness. *Federal Register, 68*(215), 62810-62811. From the
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Wiegand, R., & Brown, J. (2010). Hyaluronidase for the management of dextrose extravasation, American Journal of Emergency Medicine, 28(2), 257.e1-257.e2. doi: 10.1016/j.ajem.2009.06.010 (R)


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