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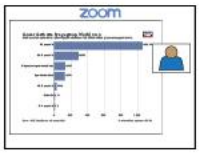

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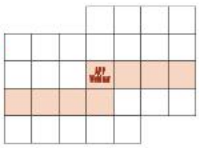

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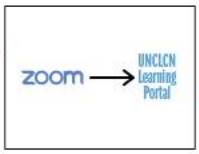

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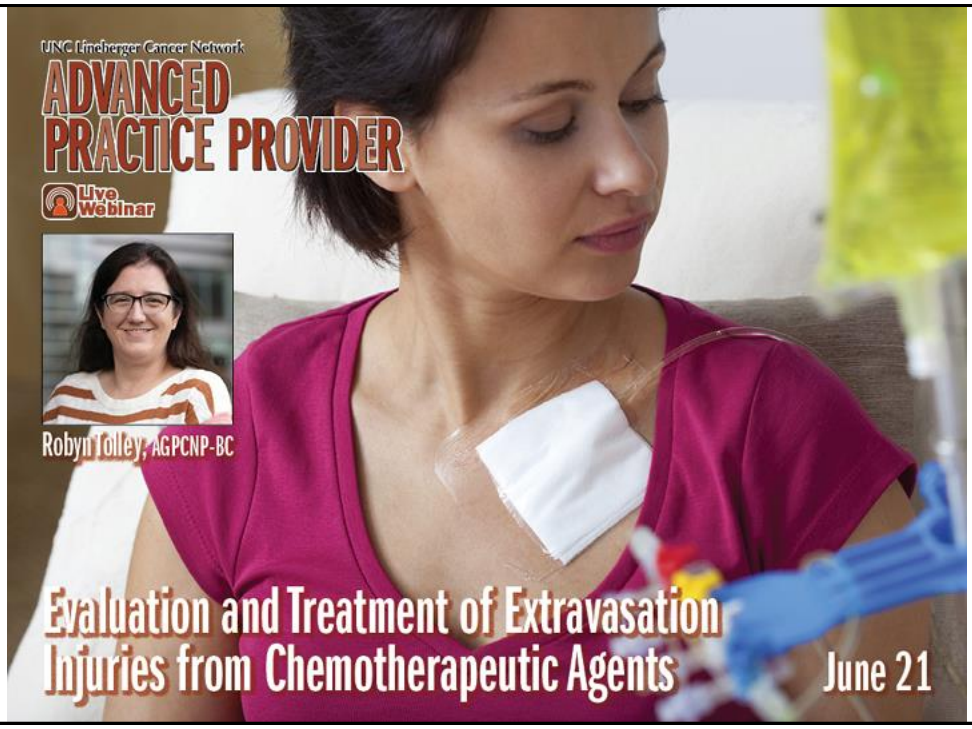

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OUR PRESENTER

Robyn Tolley, AGPCNP-BC

Robyn Tolley, AGPCNP-BC, is a nurse practitioner that works for the UNC Leukemia Program. She joined the team in May 2023, after having been a provider in the UNC Adult Oncology Infusion Clinic since 2019.

Tolley started her nursing career in hematology/oncology inpatient service in 2010 in San Antonio, TX. She has worked at UNC since December 2013 and completed her Master's of Science in Nursing at UNC Chapel Hill.

She spends most of her "leisure" time in activities with her 12-year-old twin girls, including leading girl scouts and coaching volleyball.

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5. Robyn Tolley, AGPCNP-BC, has had her OCN since 2018 and hopes to take the AOCNP exam shortly.

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4. She attended graduate school full-time while working full-time in inpatient nursing in surgical oncology.

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3. She earned her Associate's degree through Master's degree in nursing programs at UNC Chapel Hill.
2. She received her Associate's degree in nursing from Baptist School of Health Professions in San Antonio Texas. It is one of the oldest hospital-based nursing schools in Texas, founded in 1903.

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OUR PRESENTER

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2. She received her Associate's degree in nursing from Baptist School of Health Professions in San Antonio Texas. It is one of the oldest hospital-based nursing schools in Texas, founded in 1903.
1. Her professional interests in hematology/oncology care strongly lean toward symptom management.

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Extravasation is the leakage of blood, lymph, or other fluid, such as an anticancer drug, from a blood vessel or tube into the tissue around it.

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UNC CANCER CARE

Evaluation and Treatment of Extravasation Injuries from Chemotherapeutic Agents

Robyn Tolley, AGPC-NP

UNCLCN Advanced Practice Provider lecture series

June 2023

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Extravasation defined

- Extravasation is Latin based
  - “extra” refers to being outside something
  - “vas” refers to vessel
- Extravasation is a process in the body and a medical condition
- Examples in the body include movement of white blood cells to infection or injury, or cancer cells metastasizing
- The medical condition occurs when fluid infusing in an intravenous catheter leaks into surrounding tissue inadvertently

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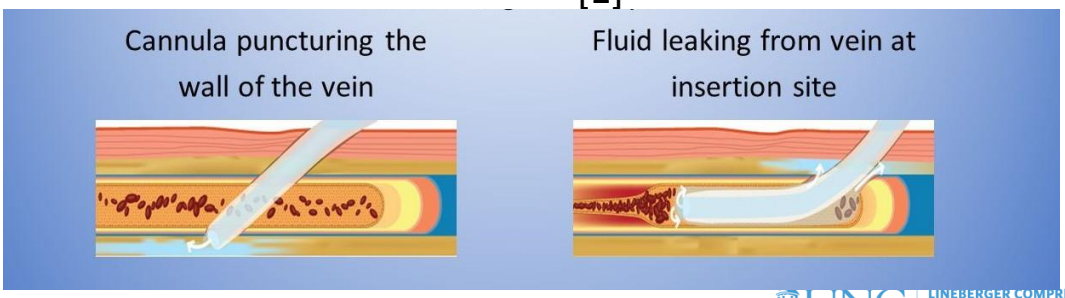
Extravasation vs Infiltration

- Extravasation is the leakage of an injected drug out of the blood vessels, **damaging the surrounding tissues** [1]
- Infiltration leakage of drug or solution into subcutaneous tissue or area surrounding the vein, **that does not irritate the tissue** [1]



Incidence

- Infusion is the principle modality for cancer treatment [7]
- There are estimated to be greater than 1 million chemotherapy infusions per day worldwide
- Unclear incidence due to no central reporting mechanism in place [7]
- Some sources cite extravasation injury in 0.1% to 6.9% of chemotherapy intravenous infusions [1]
- Extravasation is an accidental complication that may result in serious damage to patients

Complications of Extravasation

- Altered limb function[4]
- Superimposed infection [4]
- May require treatment suspension for healing [4] [4]
- Significant tissue damage [3]
  - Ulceration may require plastic surgery or skin grafts
- Pain [4]
  - May persist for several weeks or more after extravasation
  - Could require narcotic analgesia
- Impact on quality of life [3][4]
  - Can be physical (limited mobility) or psychological (disfigurement)

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Risk factors of chemotherapy extravasation

- Drug properties [1]
  - Vesicant properties
    - High vasoconstrictive potential
    - Slow drug metabolism that results in prolonged drug exposure in the extravasation area
  - Concentration
    - This includes pH and osmolarity
    - pH values that are very low (<5.5) or very high (>8.5) are particularly harmful to tissues
    - hypo- or hyperosmolar agents (<281 or >289 mOsmol/L) can both be harmful. Though hyperosmolar more so.
  - Volume
  - Duration of infusion
    - Large volumes infused over shorter period of time more likely to cause damage

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Risk factors of chemotherapy extravasation

- Patient properties [1]
  - Anatomic considerations- venous integrity, vessel size, blood flow, pre-existing pathophysiology [4]
    - Small/fragile veins
    - Hard/sclerosed veins
  - Patient education
    - signs/symptoms to be aware of and report
  - Diseases associated with altered or impaired circulation
    - Lymphedema, peripheral neuropathy, peripheral vascular disease, diabetes, Raynaud's disease
  - Agitated, confused, or with communication difficulties [4]
    - Impaired LOC
  - Previous multiple venipunctures
  - Obesity

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Risk factors of chemotherapy extravasation

- Iatrogenic properties [1]
  - Needle insertion technique
    - Higher risk with multiple venipunctures
  - Catheter selection [4]
    - Appropriate size for vessel
  - Poor location selection
    - Avoid areas of flexion or over bony prominences
    - Preferred area is forearm
  - Experience of staff
  - Initial and ongoing training for nurses [4]
  - Lack of time

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Only vesicant drugs can cause serious tissue damage when extravasated.

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Classification of Drugs

- **Irritant** [2][6]
- Drugs that cause inflammation, pain or irritation at the extravasation site without blister formation

- **Vesicant** [2][6]
- Drugs that result in tissue necrosis or formation of blisters when infused into tissue surrounding a vein

- **Non-vesicant, non-irritant or neutral** [2][6]
- Drugs that neither cause inflammation or damage upon extravasation. May cause mild inflammation or discomfort

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Classification of drugs

TABLE 1. Antineoplastic Agents Classification[1]

Vesicant		Irritant		Nonvesicant
Anthracyclines Doxorubicin Daunorubicin Epirubicin Idarubicin Anthracyclines	*Vinca alkaloids* Vincristine Vinblastine Vindesine Vinorelbine	*Alkylating agents* Carmustine Ifosfamide Streptozocin Dacarbazine Melphalan	*Topoisomerase inhibitors* Etoposide Teniposide Irinotecan Topotecan	Arsenic trioxide Asparaginase Bleomycin Bortezomib Cladribine Cytarabine Etoposide phosphate
Alkylating agents Mechlorethamine Bendamustine	*Taxanes* Docetaxel Paclitaxel	*Anthracyclines (other)* Liposomal doxorubicin Liposomal daunorubicin Mitoxantrone	*Platinum compounds* Carboplatin Cisplatin Oxaliplatin	Gemcitabine Fludarabine Interferons Interleukin 2 Methotrexate
Antibiotics Dactinomycin Mitomycin C Mitoxantrone	*Others* Trabectedin	*Antimetabolites* Fluorouracil	*Others* Ixabepilone	Monoclonal antibodies Pemetrexed Raltitrexed Temsirolimus Thiotepa Cyclophosphamide

https://www.uptodate.com/contents/extravasation-injury-from-chemotherapy-and-other-non-antineoplastic-vesicants?search=vesicants&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

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Vesicant Drugs

- **DNA binding** [2]
- Trigger cell death by apoptosis
- Remain bound to DNA of the dead cell which results in progressive tissue damage
- Progressive tissue damage may become permanent
- DNA-binding vesicants cause the most severe damage when extravasated
- Up to one third of extravasations will produce ulceration and necrosis if left untreated

- **Non-DNA binding** [2]
- Interfere with mitosis but does not bind to DNA
- Hampers DNA transcription and replication which causes cell death
- More easily metabolized in the tissue
- Damage potential is generally mild to moderate, localized, and improves with time.

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Examples of Vesicants

Alkylating agents: DNA binding
- Nitrogen mustard

Anthracyclines: DNA binding
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin

Antitumor antibiotics: DNA binding
- Dactinomycin
- Mitomycin-C

Taxanes: Non-DNA binding
- Docetaxel
- Paclitaxel

Vinca alkaloids: DNA binding
- Vinblastine
- Vincristine
- Vinorelbine
- Vindesine

https://www.elsevier.com/__data/assets/pdf_file/0020/1002287/Antineoplastic-Drug-Administration-Vesicant-and-Irritant-Agents-Skill-Oncology-COVID-19-Toolkit_140420.pdf

Irritant Drugs

- Challenge is that drugs defined as irritant or non-vesicant have been associated with extravasation injuries
- You will often find these drugs listed in vesicant category
- Typically transitory effect
  - Localized burning, pain, redness
- Does not usually lead to necrosis
- Large volumes of irritant extravasation can lead to ulceration in soft tissues [2]
- Vesicant like activity in large volumes [2]
  - Cisplatin
  - Dacarbazine
- May cause soft tissue injury [2]
  - Bendamustine
  - Irinotecan
  - Liposomal daunorubicin
  - Liposomal doxorubicin
  - Melphalan
  - Mitoxantrone
  - Oxaliplatin
  - Paclitaxel
  - Paclitaxel, nanoparticle albumin bound (nabpaclitaxel)

General care with Initial Management

- Stop the infusion immediately. The line should not be flushed. [8]
- For peripheral intravenous sites, elevate the affected extremity. [8]
- Do not remove the catheter or needle immediately. [8]
- An attempt should be made to gently aspirate the fluid remaining in the extravasated area. This is true for both peripheral and central lines. [8]
- Assess need for antidote to be administered through intravenous site. If this is not necessary, catheter or needle should be removed. [8]

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Application of Cold or Heat

- Topical application of cold packs is advised for most vesicant or irritant drugs.
- Cold therapy is advised for 15-20 minutes up to 4 times per day for 48 hours. [8]
- Intermittent cooling is thought to cause vasoconstriction, which diminishes the spread of the drug and then the extent of the local injury. [5]
- Several agents require warm compresses. This includes all vinca alkaloids and notably etoposide, gemcitabine, and oxaliplatin.
- The warmth likely increases local vasodilation, and enhances absorption of the infiltrate. [5]

Pharmacologic treatments

- No studies have been done to compare existing methods of treating extravasations. [3]
- There are several antidotes that have been studied directly with specific drugs. [3]
- Most studies performed on anthracyclines as they cause most significant tissue destruction
- Systemic glucocorticoids, anti-histamines, sodium bicarbonate, heparin, and lidocaine are considered ineffective for preventing or treating extravasation. [2]

Dimethyl sulfoxide DMSO

- Topical application of dimethyl sulfoxide (DMSO), an anti-inflammatory agent, has been shown to be effective in treating anthracycline-associated extravasation in several studies [2]
- Applied topically as cream or liquid to improve absorption of the extravasated solvent [6]
- Generally well tolerated with most reported side effect being mild local burning, tingling, or erythema [2]
- Patients do report garlic odor of breath [2]
- Studied with the following drugs-
  - Doxorubicin, epirubicin, cisplatin, ifosfamide, mitoxantrone, carboplatin, mitomycin, fluorouracil [6]
- Use 3 times per day for 3-14 days
- Used with cold compresses [6]

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Dexrazoxane

- FDA approved anti-dote for anthracycline extravasation [6]
- Was first used as cardio-protective agent for patients receiving anthracyclines [2]
- An iron chelator that prevents the formation of anthracycline-iron complexes that cause oxidative damage [6]
- Not recommended to use concomitantly with DMSO [2]
- IV infusion provided in opposite arm after extravasation. Given in daily doses for 3 days.
- First infusion should be given as quickly as possible and no later than 6 hours of extravasation. [8]
- Side effects include nausea, injection site reaction, hematological toxicity, and hepatic toxicity. [2]

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Antidotes

Antidote	Mechanism of action	Dose	Technique for use	Adverse effects	Comments
DMSO 99 % [12, 27, 37] e.g., anthracyclines, mitomycin C	-Increases the permeability of tissue by vasodilation, facilitating the systemic absorption of the extravasated drug -Neutralizes free radicals (hydroxyl) and thus reduces tissue damage -Analgesic and anti-inflammatory properties	-Four drops/10 cm^2 every 6 to 8 h for 7 to 14 days, as of the first 10 min following extravasation	-Apply to twice the size of the affected area -Apply with a glass dropper and spread with a cotton swab	-Local irritation, skin dryness, itching, peeling, tingling, redness, sensation of heat at the application site, garlic breath	-Let dry -Do not cover with an occlusive dressing (risk of blistering)
Dexrazoxane [40, 61] e.g., anthracyclines	-An iron chelator that prevents the formation of anthracycline-iron complexes and free radicals that cause oxidative damage -Stabilizes topoisomerase II and thus prevents anthracycline from damaging healthy tissue	-1000 mg/m^2 (maximum 2000 mg/dose) on days 1 and 2 and 500 mg/m^2 (maximum 1000 mg/dose) on day 3	-Administer in the arm opposite the extravasation -IV infusion over 1 h (use immediately after reconstituting) -Start treatment as quickly as possible (no later than 6 h after extravasation)	-Nausea, reaction at the injection site, hematological toxicity (↓ hemoglobin, white blood cells, neutrophils, and platelets)[a], hepatic toxicity (↑ AST, ALT, bilirubin)	-Remove any cold compresses 15 min before administering to enable the drug to quickly reach its site of action -Reduce the dose by 50 % for CrCl <40 ml/min

https://doi.org/10.1007/s00520-015-2635-7

Hyaluronidase

- Hyaluronidase is an enzyme that degrades hyaluronic acid in tissues and promotes diffusion of extravasated agent [2]
- Recommended for vinca alkaloids, etoposide, and taxanes
- Given through IV line that has extravasated or via 5 equivalent subcutaneous injections around the extravasation site [8]
- Adverse effects are local and include allergic reactions and irritation [2]

Sodium thiosulfate

- For high concentration cisplatin (remember this is an irritant until high concentration), bendamustine, and mitomycin
- Prevents tissue damage by creating an alkaline-rich site [2]
- The vesicant will bind to the sodium thiosulfate instead of the tissue, and will then be excreted in the urine [2]
- Subcutaneous injections administered around extravasated site. Divide 2ml of total volume into 0.5ml equivalent subcutaneous injections. [8]
- No reported adverse reactions

Antidotes

Hyaluronidase [23, 27] e.g., vinca alkaloids	-Enzyme that breaks down hyaluronic acid, chondroitin acid, and mucoitin sulfate in connective tissue, improving absorption	-Up to 1500 units -Hyalase™: 1500-unit vial to be diluted with 1 ml of sterile water for injection or NaCl 0.9 %	-Five subcutaneous 0.2-ml injections around the periphery of the extravasation site with a 25-G needle or smaller -Change the needle for each injection	-Hypodermoclysis, allergic reactions, local irritation	
Sodium thiosulfate [23, 26, 27, 62] e.g., mechlorethamine	-Prevents the tissue damage induced by mechlorethamine by providing a substrate for alkylation in subcutaneous tissue	-2 ml of an isotonic solution, that is, 0.17 M (1.6 ml sodium thiosulfate 25 % + 8.4 ml sterile water for injection) for each milligram of extravasated mechlorethamine	-Subcutaneous injections in and around the extravasation site -Must be administered immediately after extravasation	N/A	-Mechlorethamine is no longer commercially available

https://doi.org/10.1007/s00520-015-2635-7

Plastic surgery consult

- **Indications for consult for evaluation- [8]**
  - Caustic infiltrate of IV site
  - Decreased sensation of affected extremity
  - Development of blister necrosis
  - Patient is over 70, less than 10 years of age
  - Large amount of agent extravasated
  - Complaint of severe pain after initial injury
  - Minimal healing evident 1-3 weeks after initial injury
- **Indications for surgery in extravasation include full thickness skin necrosis, chronic ulcer, and persistent pain.**
  - Surgical interventions include excision and possible skin grafting [2]

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"An ounce of prevention is worth a pound of cure."
— Benjamin Franklin

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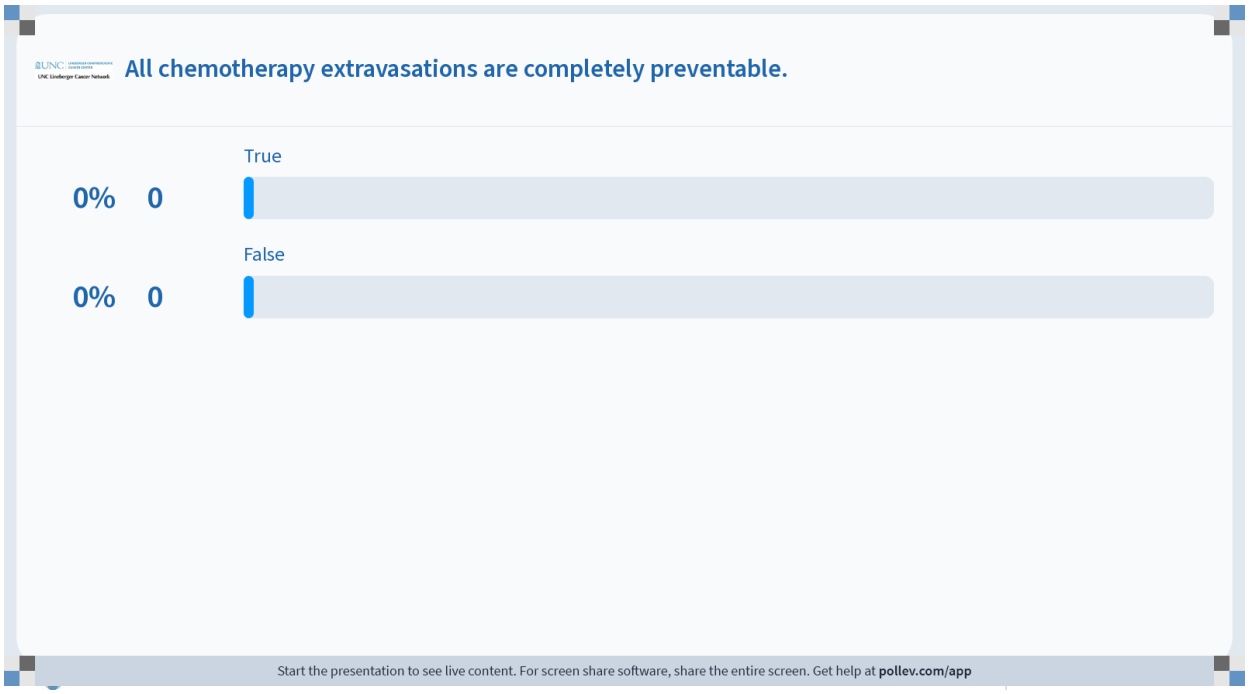

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Preventive Measures

- Most extravasations can be prevented with systemic implementation of careful, standardized, and evidence-based administration techniques. [5]
- Staff should have familiarity with extravasation management standard guidelines. [5]
- Medications to manage extravasation should be readily available. [5]
- Ongoing training for staff regarding device placement and management should be occurring. [5]

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Preventive Measures

- **Associated with Intravenous site-** [2]
- Select large veins in the forearm for a small peripheral venous catheter.
- Avoid insertion sites near tendons, joints, and neural structures.
- Do not use the inner wrist or antecubital fossa (inside elbow) because a cannulation in the bending zone is more likely to dislodge the catheter.
- Avoid the back of the hand and wrist because the lack of tissue there means that the underlying structures are more easily damaged during extravasation and the risk of compartment syndrome is higher.
- Cover the injection site with a transparent dressing (must be visible at all times).
- If there is any doubt, change the cannulation site.
- A venogram or chest X-ray could be done if there is any doubt that a central venous line is properly positioned.
- Use a stabilization system with extension tubing for peripheral lines.

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Preventions measures

- **Associated with administration**- [2]
- Check for blood return before administering chemotherapy to ensure that the line is properly placed in the vein.
- Use a central line if a vesicant must be administered for longer than 30 to 60 min.
- When administering vesicants via peripheral lines, use a compatible primary solution.
- Continuously monitor the injection site (check for swelling, inflammation, redness) before and during the entire chemotherapy infusion.
- Recognize the potential signs and symptoms of extravasation: pain; redness; edema; erythema; induration; lack of blood return; resistance to irrigation; resistance or change in infusion rate; pain in the shoulder, neck, or ear on the side of a central venous catheter; and leaking of fluid from around the dressing securing the IV device.

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Prevention considerations for providers

- Discuss risks of extravasation and tissue damage with patients prior to start of treatment.
- Assess patient difficulty with obtaining stable intravenous access.
- Educate patient and family regarding frequency of intravenous access required for treatment plan.
- Engage patient to ask questions regarding concerns of central line placement if they exist.

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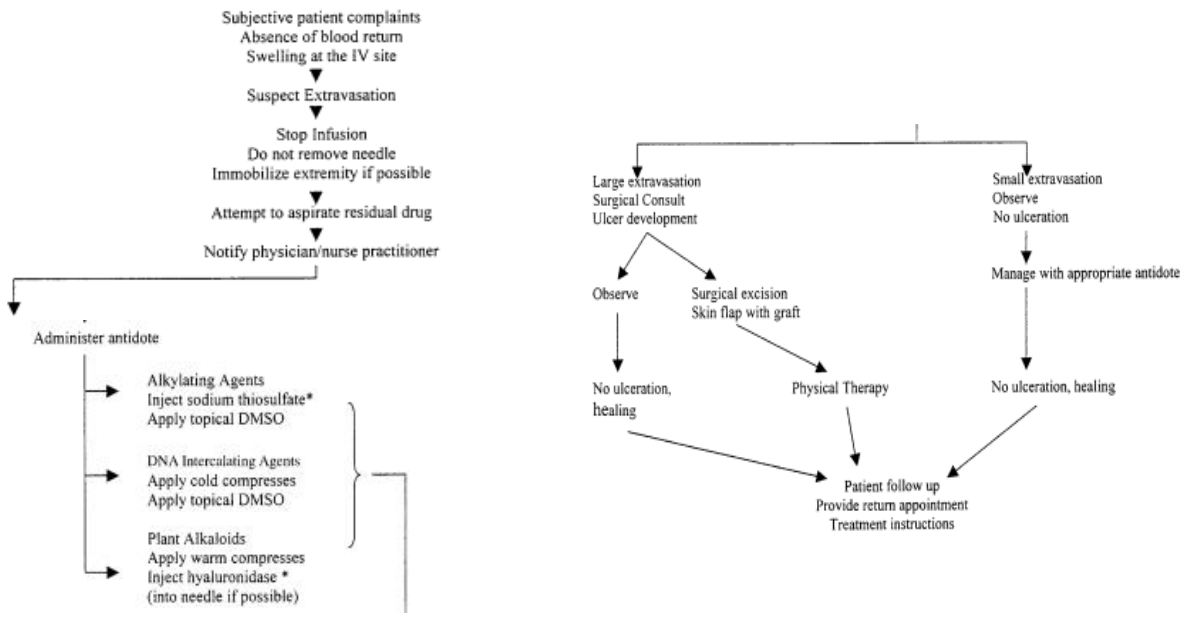

doi:10.1053/jpon.2000.8063 48

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UNC Lineberger Cancer Network

The Telehealth Team

Tim Poe, Director

Veneranda Obure, Technology Support Specialist

Jon Powell, PhD, Continuing Education Specialist

Oliver Marth, Technology Support Technician

Andrew Dodgson, DPT, Continuing Education Specialist

Nadja Brown, Interim Administrative Support Specialist

Patrick Muscarella, Technology Support Technician

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UPCOMING LIVE WEBINARS

RESEARCH TO PRACTICE
Live Webinar

June 28
12:00 PM

Lymphoma Management in North Carolina: Updates for 2023
Natalie Grover, MD

PATIENT CENTERED CARE
Live Webinar

July 12
12:00 PM

ePROs Monitoring in Thoracic Surgery and Oncology Patients
Gita Mody, MD, MPH

ADVANCED PRACTICE PROVIDER
Live Webinar

July 19
4:00 PM

Clinical Trials for the APP
Clarissa Urban, PA-C

Complete details on upcoming Live Webinars:
learn.unclcn.org/live-webinars

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SELF-PACED, ONLINE COURSES

ADVANCED PRACTICE PROVIDER
Self-Paced, Online Course

Oncologic Emergencies, A Deeper Dive: Neutropenic Fever, Tumor Lysis Syndrome, and Cord Compression
Laura Blanchard, MPAP, PA-C

SOUTHEASTERN AMERICAN INDIAN CANCER HEALTH EQUITY PARTNERSHIP
Self-Paced, Online Course

Partnership for Native American Cancer Prevention
Francine C. Gachupin, PhD, MPH

PATIENT CENTERED CARE
Self-Paced, Online Course

Where the Rubber Meets the Road: Community: Inclusive Interventions to Achieve Equity in Cancer Care
Samuel Cykert, MD and Christina Yongue, MPH, MCHES

Today's webinar will be available in about one month as a ***FREE***, Self-Paced, Online Course

Complete details on Self-Paced Online Courses:
learn.unclcn.org/spoc

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THANK YOU FOR PARTICIPATING!

UNC Lineberger Cancer Network

Email: **unclcn@unc.edu**

Call: **(919) 445-1000**

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