Guidelines on treatment of extravasation with cytotoxic drugs

Please refer to local policy for extravasation of non-cytotoxic drugs.

Extravasation is defined as the accidental leakage from its intended compartment into the subdermal or subcutaneous tissue surrounding the administration site. Usually, this occurs when intravenous (IV) medication passes from the blood vessel into the tissue around the blood vessels and beyond. They can occur in peripheral and central vascular access devices. The degree of tissue damage can range from a very mild skin reaction to sever tissue necrosis, the severity depends on the drug, concentration and quantity of drug extravasated.

Classification of Extravasation

Extravasation with cancer drugs can be classified into 5 categories, according to the reaction that is caused by the substance passing into the surrounding tissue. In these guidelines only cancer therapies will be classified, however they are not the only drugs that cause damage when extravasated and non-cancer therapies (eg hypertonic solutions, amphotericin, parental nutrition, antibiotics etc) can be equally as destructive, please refer to local hospital policies for management of extravasation with these drugs.

Definitions:

1. **Vesicant:** An agent that has the potential to cause pain, inflammation, blistering and irreversible tissue damage, including necrosis and loss of limb function and mobility.
2. **Exfoliants:** An agent that is capable of causing inflammation and skin shedding, but less likely to cause tissue damage.
3. **Irritant:** An agent that causes pain and inflammation at the administration site and / or along the vein, but rarely results in irreversible tissue damage.
4. **Inflammatory agents:** An agent capable of causing mild to moderate inflammation.
5. **Neutral:** An inert or neutral agent that does not cause inflammation or damage.

List of cytotoxic agents & their classification

Vesicants	Exfoliants	Irritants	Inflammatory agents	Neutrals
Amsacrine	Aclarubicin	Bortezomib	Etoposide phosphate	Arsenic trioxide
Bendamustine*		Cabazitaxel	Eribulin	Asparaginase
Carmustine	Cisplatin	Carboplatin	Fluorouracil	Bevacizumab
Dacarbazine	Daunorubicin (liposomal)	Etoposide	Methotrexate	Bleomycin
Dactinomycin	Docetaxel	Irinotecan	Pemetrexed	Cetuximab
Daunorubicin	Liposomal Doxorubicin (ICaelyx)	Ixabepilone	Raltitrexed	Cladribine
Doxorubicin	Floxuridine	Teniposide	Temsirolimus	Cyclophosphamide
Epirubicin	Oxaliplatin			Cytarabine
Idarubicin	Topotecan			Fludarabine
Mechlorethamine				Gemcitabine
Mitomycin				Ifosfamide
Mitoxantrone				Interferons
Mustine				Interleukin 2
Paclitaxel *				Ipilimumab
Streptozocin				Melphalan
Trabectedin				Monoclonal antibodies
Treosulphan				Nivolumab
Vinblastine				Pembrolizumab
Vincristine				Pentostatin
Vindesine				Rituximab
Vinflunine				Thiotepa
Vinorelbine				Trastuzumab

- * some texts class these as irritants / vesicants
- As new drugs are being licensed regularly, please liaise with your local pharmacists to confirm vesicant nature of any new drugs, prior to drug administration.

Risk factors

Patients receiving cancer treatment may have multiple risk factors that make IV administration very difficult. In addition, there may be factors relating to equipment / material used, concomitant medications and the treatment themselves. Some of the most common factors known to increase the risk of extravasation are listed below:

Patient factors

- small blood vessels (eg infants & young children, adults who have had previous chemotherapy)
- fragile veins (eg elderly / those on medications such as steroids)
- hard / sclerosed veins (eg patients who have had prior chemotherapy)
- mobile veins
- impaired circulation (lymphoedema, obstructed vena cava)
- pre-existing conditions (eg diabetes, peripheral vascular disease, Raynaud's disease, radiation damage)
- thrombocytopenia
- obesity
- trouble reporting symptoms early (eg sedated / confused / babies)

Personnel factors

- untrained / inexperienced
- lack of experienced staff to provide support
- multiple cannulation / venepuncture sites, (do not insert a cannula below failed venepuncture sites)
- site of cannula, the risk serious tissue damage increases when veins over vital nerves and tendons are used (eg ante-cubital fossa)

Equipment / Material factors

- catheter size and gauge

Treatment factors

- ability to bind directly to DNA
- ability to kill replicating cells
- ability to cause tissue or vascular dilation
- pH
- osmolality
- characteristics of diluent

Prevention:

- Training - only staff educated in the techniques of IV administration and have received specialist training and are competent should handle and administer systemic cytotoxic drugs
  - all staff should receive training in extravasation prevention, recognition and management
- Patient education – see below
- Equipment selection -
  - for peripheral access, use of an appropriate gauge cannula for the flow rate and size of veins (eg a small bore flexible polyethylene or teflon cannula, 1.2-1.5cm long)
  - a steel / butterfly needle should not be used to administer any cytotoxic drugs
  - use a clear dressing to secure the cannula (to allow for constant inspection)
  - secure infusion line, but never cover the line with a bandage (the insertion point must always be visible)
- Vein selection for peripheral administration -
  - try to use the forearm
  - avoid small and fragile veins
  - avoid insertion on limbs with lymphoedema or neurological weakness
  - avoid veins next to joints, tendons, nerves or arteries
  - avoid the antecubital fossa
    (for a more detailed overview of vein selection, please refer to 'Vein Selection Procedure', page 4
  - if a first attempt to insert a cannula failed, the second should be made closer to the heart (ie moving up the arm and thus avoid administering cytotoxic drugs below a previous venepuncture site

A Central Venous Access Device (CVAD) should be considered if veins are difficult to access or regimens are known cause pain during infusion or chemical phlebitis (eg FEC-D, ABVD, Oxaliplatin etc)

Vein Selection Procedure for peripheral cannula

Assess veins in both arms and hands Do not use veins in compromised limbs / lower extremities		
	Criteria for vein selection	Appropriate choice of venepuncture site
Most Desirable	IDEAL VEIN / BEST LOCATION large, soft, resilient veins in forearm	Forearm
↓	IDEAL VEIN / LESS DESIRABLE LOCATION large, soft, resilient veins in hand	Hand
↓	SATISFACTORY VEIN / BEST LOCATION small, thin veins in forearm	Forearm
↓	SATISFACTORY VEIN / UNDESIRABLE LOCATION small, thin veins in hand, veins in forearm not palpable or visible	Hand
↓	UNSATISFACTORY VEIN / UNDESIRABLE LOCATION small, fragile veins, which easily rupture in forearm /hand	Consider central venous access
↓ **Least Desirable**	UNSATISFACTORY VEIN / UNDESIRABLE LOCATION **Ante cubital fossa**, veins in forearm or hand not that are not palpable or visible	Consider central venous access

Administering Intravenous treatment:

- become familiar with the manufacturers' recommendations for administration of each drug
- dilute drugs to the recommended concentration and give at the appropriate rate
- where possible use a freshly inserted cannula and resisting of the cannula is as per hospital policy
- before administering therapy, flush the line with sodium chloride 0.9% or glucose 5% (as well as between infusions)
- check blood return from the cannula or CVAD, prior to administration. If no blood return from a CVAD, do not administer an *'Exfoliant or Vesicant'* drug through this line until further investigations have been completed to ensure that the line is intact and in the correct position, eg CXR +/- try urokinase as per local policy
- consider the order of drug administration, ie vesicants should be administered first, then exfoliant, then irritant, etc, Please refer to the cytotoxic drugs classification list for guidance of order to give when 2 or more vesicant drugs are being administered,
  For example: CHOP: administer anthracyclines before vinca alkaloids
  ABVD: administer doxorubicin, vincristine, bleomycin and dacarbazine. Whilst dacarbazine is vesicant it is deemed safer practice to administer all short infusions first and leave drug with longer infusion time to last.
- ensure that the cannula is secure during drug administration
- never cover the insertion point
- if in doubt, recannulate

Monitoring during IV treatment:

- check for swelling, inflammation, redness and pain around the cannula site during administration of drugs apply warmth to increase vasodilation
- check blood return from cannula when vesicants are administered
- question the patient about the possible symptoms
- do not allow patients receiving vesicant & exfoliant drugs to leave the clinical area (ambulatory chemotherapy infusions via appropriate devices are excluded)
- for vinca alkaloid infusions, stay and observe throughout administration.

Patient information

Informing patients of the possibility of extravasation is critical prior to **ALL** cycles of cancer therapy, as they can be relied upon to report symptoms critical in its early recognition. Emphasising the need for them to inform staff immediately if they experience a burning, stinging, pain or change in sensation at or around the cannula site and along the vein, or if they notice any swelling during administration.

Signs and symptoms of extravasation - Treat as a medical / nursing emergency

The initial symptoms are subtle and can be similar for the extravasation of different agents, however the progression for these different agents differs greatly, eg irritants V's vesicants, particularly relating to permanent damage to the tissue. It is estimated that one third of vesicant extravasations give rise to ulceration, in combination with pain and necrosis and can be an indication for surgical intervention. They can lead to more hospital consultations, the need for physical therapy, psychological consequences (eg distress/anxiety), reduced mobility, etc.

Check for extravasation if you observe *or* the patient complains of:

- subtle changes in patient expression that gives a forewarning to discomfort
- infusion devices that alarm and indicate a high venous pressure
- a burning or stinging pain that occurs during administration and gradually stops after stopping drug administration
- an ongoing discomfort or pain, which can range from mild to intense at or around the cannulation site (ensure it is not a 'Vein Pain Reaction', caused by drugs: Oxaliplatin, Dacarbazine, Gemcitabine)
- redness at the cannulation site (not to be confused with anthracycline flare)
- swelling or signs of drug leakage
- drip flow rate is reduced or stops (ensure is not venospasm / venoconstriction)
- resistance from the syringe plunger (ensure is not venospasm / venoconstriction)
- lack of blood return from the cannula (not a lone indicator of extravasation)
- erythema / oedema may only occur several hours after the patient initially complained or the infusion was completed, blistering may only occur several days after the event

On their own, none of these are confirmation of an extravasation but they should be treated with concern and warrant further examination. Please refer to section *'Distinguishing Extravasation from other Conditions'* page 9.

If in doubt, stop infusion / administering drug, await a second opinion from a more experienced chemotherapy trained colleague (ie Ward Sister, Chemotherapy Specialist Nurse or their deputies) or seek medical advice.

Management of Extravasation

If extravasation does occur, prevention of serious injury and tissue damage becomes the main focus of those involved in the patient management. Swift action is important to limit the damage (treatment should be administered within 1 hour), however extravasations may only become apparent 1-4 weeks after drug administration. All staff should be aware of the extravasation policy and know the contents and whereabouts of the extravasation kit.

No matter what the nature of the drug, if extravasation is suspected the initial response remains the same. The most important thing is to limit the amount of drug extravasating into the surrounding tissue

Flow Chart for management of extravasation via a Peripheral Cannula

Suspected extravasation – treat as medical / nursing emergency

- Stinging/burning/pain at the site
- Swelling and redness
- Drug leakage
- Reduced IV flow rate + / or resistance
- Lack of blood return from cannula

- Stop the infusion / injection and Assess
- Ask a colleague to summon a doctor & collect the extravasation kit
- Take care not to apply unnecessary direct manual pressure to the extravasation area
- Disconnect the infusion, aspirate as much of the drug as possible with a 10ml syringe,
- Mark the affected area
- Remove the cannula

Is the drug vesicant?

Yes

Vinca-alkaloids (eg vinblastine, vincristine, vindesine, vinorelbine)

- Apply warm pack
- Inject hyaluronidase 1500iu dissolved in 1ml water for injection, 0.2ml intradermally or s/c 3-5 times,around site. Clean skin first and change needle after each injection.
- Within one hour of extravasation.
- Cover with sterile gauze dressing
- Elevate limb

Other vesicant drugs

Apply cold pack.
Cover with sterile gauze dressing.
Elevate limb.

No

Is the drug exfoliant?

No

Other non-vesicant drugs

Apply cold pack.
Cover with sterile gauze dressing.
Elevate limb.

Yes

Has more than 10mls extravasated?

No

Yes

If Oxaliplatin

- Apply heat pack
- Infiltrate with 200mls 5% glucose s/c
- Inject hyaluronidase 1500iu dissolved in 1ml water for injection, 0.2ml intradermally or s/c 3-5 times,around site. Clean skin first and change needle after each injection. Do within one hour of extravasation.
- Cover with sterile gauze dressing
- Elevate limb

If Other exfoliant

Apply cold pack.
Cover with sterile gauze dressing
Elevate limb.

1. Administer pain relief (systemic / topical) if required
2. If vesicant or exfoliant, inform patients Consultant, contact on-call Plastic surgery SpR for advice & consideration of 'flush-out', within one hour
2. Complete extravasation documentation, incident form and record in patient's notes (send copy to Lead Chemotherapy Nurse)
3. Give patient an information sheet, care of the site and follow up appointments
4. Review at 24hour, 3 days & 7 days and continue until injury has resolved
5. If chemotherapy is to be continued where possible avoid using extravasated limb (seek advice from Vascular Access Team, Consultant and/or Lead Chemotherapy Nurse or CNS's

Flow chart for management of extravasation via a Central Venous Access Device

Suspected extravasation – treat as medical / nursing emergency

- Stinging/burning/pain at the entrance site or along the track of the catheter
- Swelling and redness
- Drug leakage
- Reduced IV flow rate + / or increased resistance
- Lack of blood return, refer to Central Venous Access Device policy & do not administer Vesicant / Exfoliant drugs until further investigation.

↓

1. Stop the infusion / injection and Assess
2. Ask a colleague to summon a doctor & collect the extravasation kit
3. Disconnect the infusion, with a 10ml syringe aspirate as much of the drug as possible and document the amount (take care not to apply unnecessary direct manual pressure to area of extravasation.
4. Mark the affected area

↓

Is the drug vesicant?

Yes

↓

Vinca-alkaloids (eg vinblastine, vincristine, vindesine, vinorelbine)
Apply warm pack (2-4hrs).
Mark area

Seek advice of Plastics team & Vascular Access team

Other Vesicant drugs
Apply cold pack
Mark area

Seek advice of Plastics team & Vascular Access team

No

Is the drug Oxaliplatin?

Yes

↓

If Oxaliplatin
Apply heat pack

Seek advice of Plastics team & Vascular Access team

No

↓

Apply Cold Pack

Seek advice of Plastics team & Vascular Access team

1. Administer pain relief (systemic / topical) if required
2. Inform patients Consultant, contact on-call Plastic surgery SpR
2. Complete extravasation documentation, incident form and record in patient's notes, send copy to Lead Chemotherapy Nurse
3. Give patient an information sheet, care of the site and follow up appointments
4. Review at 24hours, 3 & 7 days and continue until injury has resolved
5. If chemotherapy is to be continued seek advice from Vascular Access team / Consultant / Lead Chemotherapy Nurse or CNS's

Suggested contents of an Extravasation kit

Extravasation policy	Drug chart and pen
Cold pack (ensure availability in fridge)	Hot pack
Hyaluronidase 1500iu injection	Water for injection
2ml syringes x 2	10ml syringes
25ga needles x 10	23ga needles x 2
Alcohol swabs	
Gloves & Apron	Sterile Gauze swab & tape
Patient information leaflet	Consent form for photographs

Cold Pack = Localise / Cooling

Use cold packs to limit the spread of infusate. It used to be thought that cold limited the spread through vasoconstriction; however another theory is that there is decreased cellular uptake of drug at lower temperature. Do not put the cool pack into direct contact with skin (so as to prevent a frost bite type reaction). Apply for 20 mins, 4 times daily for 1-2 days.

Warm Pack = Disperse & Dilute

Appropriate for the extravasation of vinca alkaloids and oxaliplatin. Use warm packs to prompt vasodilation and encourage blood flow in the tissues, thereby spreading the infusate around. Do not put the heat pack into direct contact with skin (so as to prevent a burn reaction). Apply for 20 mins, 4 times daily for 1-2 days.

Distinguishing extravasation from other conditions:

Characteristic	Flare Reaction	Vessel irritation	Venous shock	Extravasation
Presenting symptoms	Itchy blotches or hives, pain and burning uncommon	Aching and tightness	Muscular wall of blood vessel in spasm	Pain and burning are common at injection site; stinging may occur during infusion
Colouration	Raised red streak, blotches or 'hive-like' erythema along the vessel;, diffuse or irregular pattern	Erythema or dark discolouration along vessel		Erythema around area of needle or around the venepuncture site
Timing	Usually appear suddenly and dissipates within 30-90 minutes	Usually appears within minutes after injection. Colouration my only appear later in the process	Usually appears right after injection	Symptoms start to appear right after injection, symptoms endure
Swelling	Unlikely	Unlikely		Occurs often: does not dissipate for several days
Blood return	Usually, but not always intact	Usually, but not always intact	Often absent	Usually absent or sluggish

Administering Hyaluronidase – administer by nurse / doctor competent to treat patient
Hyaluronidase may be indicated for suspected or known extravasation of: dextrose in concentrations of >10%, parental nutrition, solutions containing potassium or calcium, antibiotics and for vinca alkaloid extravasations.
Steps for administrations:

1. inform patient of procedure
2. ensure hyaluronidase is prescribed before administration
3. should be administered within 1 hour of extravasation for best results
4. dilute1500iu of hyaluronidase in 1ml of water for injection,
5. With a 25g needle, administer intradermally or subcutaneously around the peripheral extravasation (having cleaned the skin first), inject 0.2ml at 3-5 separate sites depending on size of extravasation Change the needle after each injection,
6. document procedure (take photographs if camera available, patient needs to sign a consent form).

Dexrazoxane (Savene)
Dexrazoxane is a DNA topoisomerase II drug that is licensed in the event of an anthracycline extravasation. By binding to iron complexes (Fe3+) before anthracyclines enter cells, dexrazoxane prevents the formation of the Fe- anthracycline complex. This prevents free radical release and cell damage. Therefore nearly eliminating the need for surgery (53/54; 98%) in severe anthracycline extravasation.

Dexrazoxane is cytotoxic and must be prepared in a pharmacy aseptic compounding unit.

Patient needs to be consented

Dexrazoxane is administered once daily for a 3-day treatment cycle as follows:

- First Dose Within 6 hours at 1000mg/m^2
- Second dose Day 2: 24 (±3) hours after day 1 at 1000mg/m^2
- Third Dose Day 3: 48 (±3) hours after day 1 at 500mg/m^2

As an intravenous infusion over 1-2 hours into a large vein in an extremity/area other than the one affected by the extravasation.

If cooling procedures have been used (e.g. ice packs) – they should be removed at least 15 minutes prior to dexrazoxane administration in order to allow sufficient blood flow

Dexrazoxane should be used immediately after preparation, or within 4 hours if stored at 2 to 8°C

Dimethylsulfoxide (DMSO) use is NOT recommended in conjunction with SAVENE®

Note : it is prepared in a glass bottle, care required during transportation and the 'hanger' provided will require re-enforcing for administration.

Side effects : Refer to SpC
Fatigue, Nausea, Myalgia, Alopecia, Pruritis

Caution : Patients taking warfarin will require closer monitoring of clotting levels

Contraindications : Hypersensitivity to the active substance or to any of the excipients
Women of childbearing potential not using contraceptive measures
Breast-feeding
Concomitant vaccination with yellow fever vaccinontraindications :

Patient Extravasation information leaflet (available on aria, so that patient demographics can be uploaded)

Date

Dear

Whilst having your chemotherapy, some of the drug has leaked outside of the vein into the surrounding skin, this is called an **extravasation.** It is a rare but known complication of chemotherapy and symptoms may occur during the infusion or even several hours or days after the chemotherapy infusion has been completed.

Name of drug that has Extravasated: _____

The nurse has given you the recommended treatment for the extravasation, which is:

The nurse will arrange appointments for review of the extravasation area,

Date: Time:
Date: Time:
Date: Time:

What do I need to do?

a. check the area daily and report any changes: in skin colour - increased redness, increased swelling, peeling/flaking or blistering of the skin, increased discomfort/pain and reduced mobility of joint to the nursing team at your hospital
b. apply hot or cold pack (delete as applicable) for 20mins, 4 times per day, until swelling/redness has disappeared. Please ensure that the pack is covered with a cloth and not applied directly to area, to prevent a burn/frost bite reaction
c. take mild painkillers if required, eg paracetamol 1000mg maximum 4 times per day, the nurse/doctor will advise

If you have any concerns or would like further advice, please telephone:

General Practitioner / Primary Care Extravasation letter (available on Aria, so demographic details can be uploaded)

Date

Dear

Re: Patient Demographics

Whilst receiving their course of chemotherapy today, which was '*Regimen, Cycle number & day number',* an extravasation occurred on the above named patient. This is a *'name category'* drug and *'write details of potential outcome for drug here'.*

Please see the attached letter, which details the information, treatment and advice given to the patient.

Should they attend your clinic with increased discomfort, peeling, blistering of the skin or if you have any concerns or require further advice about the recovery time for this extravasation, please contact:

Name of department:

Telephone Number:

Documentation and Reporting

Each incident of extravasation must be thoroughly investigated and reported. Documentation serves several purposes:

- to provide an accurate account of what happened (especially in the event of litigation)
- to protect healthcare professionals involved (showing they followed procedure)
- to gather information on extravasations, how and when they occur – for audit purposes
- highlight and possible deficits in practice which require review

The following details should be documented

- patient name & number
- clinical area
- date & time of extravasation
- name of extravasated drug and volume
- signs & symptoms (eg size of extravasation, colour of skin, degree of pain)
- Grading Scale for monitoring extravasation
- description of IV access (venepuncture site, size of cannula, number of attempts at obtaining venous access & positions, type of central line, drugs administered and sequence, if bolus / infusion, blood return, if infusion device use – type & serial number)
- extravasation area (approximate amount of drug extravasated, size – diameter, length & width, depth if possible, appearance, photograph – need to obtain patient consent)
- step-by-step management with date and time of each step performed and medical notification (aspiration possible – including amount and location, cold/heat, antidote, referral details)
- patient's complaints, comments, statements
- indication that patient information sheet given to patient
- follow-up instructions given to patient, GP and Community Staff
- name of all professionals involved in the patient management
- signature of nurse

In addition to the initial documentation, the extravasation should be checked and any changes documented. Any oedema, erythema, stinging, burning, pain, or fluid leakage at insertions site should be included in this report.

Incident form / datix completed as per local policy.

Grading Scale for monitoring extravasation

Grade	1	2	3	4	5
Skin colour	Normal	Pink	Red	Blanched area surrounded by red	Blackened
Skin integrity	Unbroken	Blistered	Superficial skin loss	Tissue loss & exposed subcutaneous tissue	Tissue loss & exposed bone / muscle within necrosis / crater
Skin temperature	Normal	Warm	Hot		
Oedema	Absent	Non pitting	Pitting		
Mobility	Full	Slightly limited	Very limited	immobile	
Pain	Grade using a scale of 0-10, where 0 = no pain & 10 = worst pain				
Temperature	Normal	Elevated (indicate actual temperature)			

References:

1. Schulmeister, L. Vesicant chemotherapy extravasation management. *British Journal of Nursing* 2011 (Intravenous supplement 20(19): S6-S12)
2. Allwood, Stanley, Wright The Cytotoxic Handbook, 4th edition
3. Ener RA, meglathery SB, Styler M. Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004;15:858-862
4. European Oncology Nurses Society *Extravasation Guidelines* 2007
5. Jones L, Coe P. Extravasation. *European Journal of Oncology Nursing* 2004,8:355-358
6. McCaffrey Boyle D, Engelking C, Vesicant extravasation: myths and realities. *Oncology Nursing Forum* 1995;22(1):57-67
7. National Extravasation Information service Web site. (www.extravasation.org.uk)
8. Pan-Birmingham NHS. Guidelines for the Management of Extravasation
9. Pan London Guidelines for the safe Prescribing, Handling and Administration of Cytotoxic Drugs
10. Savene Summary of Product Characteristics SmPC February 2010
11. United Kingdom Oncology Nursing society, *Anthracycline Extravasation Management Guidelines* 2007

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