Guideline for the management of extravasation of a cytotoxic agent or a monoclonal antibody used in the treatment of malignant disease

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

Introduction
The purpose of this guideline is to provide clear guidance on the causes, prevention, recognition and management of an extravasation of a cytotoxic agent or a monoclonal antibody used in the treatment of malignant disease in the patient over the age of 16 who is being cared for in adult services. Extravasation is an oncology emergency and therefore it is imperative that it is recognised, diagnosed and treated swiftly to minimise the potential for injury.

This guideline is for use by the following staff groups:
This guideline is relevant to all chemotherapy nursing and medical personnel working with patients over the age of 16 who are being cared for in adult services within Worcestershire Acute Hospitals NHS Trust.

Lead Clinician(s)
Sue Sharp Chemotherapy Project Nurse

Initially Approved by Cancer Services and Clinical Haematology Directorate Meeting on: 29th November 2010
Approved by accountable director on: 2nd January 2015
This guideline should not be used after end of: 2nd January 2016
Key Amendments to Document

<table>
<thead>
<tr>
<th>Date</th>
<th>Amendment</th>
<th>By</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2012</td>
<td>Addition of new agents</td>
<td>S.Sharp</td>
</tr>
<tr>
<td>March 2012</td>
<td>Changes Approved by Cancer Services and Clinical Haematology Directorate Meeting</td>
<td>S.Sharp</td>
</tr>
<tr>
<td>May 2012</td>
<td>Minor amendments</td>
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<tr>
<td>September 2012</td>
<td>Changes to layout and font colourings addition of additional agents</td>
<td>S.Sharp</td>
</tr>
<tr>
<td>September 2014</td>
<td>Document extended for 3 months</td>
<td>S. Shafeek</td>
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</table>
Guideline for the management of extravasation

Definition
Extravasation is the accidental or inappropriate process of one substance leaking from a vein into the surrounding tissues (Jones L & Coe P 2004), this term is a generic term for this process however the scope of this guidance is when the substance involved is a cytotoxic agent or a monoclonal antibody used in the treatment of malignant disease.

A broader definition of extravasation includes the resulting injury. Depending on the substance that extravasates into the tissue, the degree of injury can range from a very mild skin reaction to severe necrosis. (McCaffrey Boyle D, Engelking C 1995).

The extent of injury has is determined by the following factors;
- the type of drug which extravasates
- the concentration and volume of drug in the tissue
- the location of the extravasation
- the co-morbidities and other patient factors

Although an uncommon event occurring in 0.5-5% of patients receiving chemotherapy an extravasation injury has the potential for significant impact on the patients quality of life (Allwood M, Stanley A, Wright P (Eds) 2002).

This guideline has been developed in accordance with the latest scientific understanding and best evidence to date in combination with health professional consensus to ensure that the patient receives optimal treatment. However this is a complex subject where there is limited evidence due to lack of research and a low incidence of reporting which is difficult to ascertain whether this is a true reflection of the incidence of extravasation and subsequently obtaining consensus can be challenging. This guideline has been developed by reviewing other health care providers’ guidelines, national and international guidance, published papers and reviewing individual drug monographs and obtaining specific advice from manufacturers if available.

Classification of Cytotoxic Agents
For the purpose of this document as previously stated the classification will relate to cytotoxic agents however it is important to note that some non-cancer therapies when extravasated have the potential to cause serious injury however this is beyond the scope of this document.

The classification of cytotoxic agents is based on the potential to cause tissue damage if extravasated:-

Vesicants: Drugs which are capable of causing pain, inflammation and blistering of the local skin, underlying structures, leading to tissue death and necrosis.

Exfoliants: Drugs which are capable of causing inflammation and shedding of the skin but less likely to cause tissue death

Irritants: Drugs which are capable of causing inflammation, irritation or pain at site of extravasation but rarely cause tissue breakdown.

Inflammants: Drugs which are capable of causing mild to moderate inflammation and flare in local tissues

Neutrals: Inert or neutral compounds that do not cause inflammation or damage

Classification of drugs commonly used in chemotherapy Regimes
### Vesicants
- Abraxane
- Amsacrine
- Cabazitaxel
- Carmustine
- Daunorubicin
- Dacarbazine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dacarbazine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dacarbazine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dacarbazine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dacarbazine
- Dactinomycin

### Exfoliants
- Cisplatin
- Docetaxel
- Liposomal Daunorubicin
- Liposomal Doxorubicin
- Mitoxantrone
- Oxaliplatin
- Topotecan
- Daunorubicin
- Carmustine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dactinomycin
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- Carmustine
- Dactinomycin
- Daunorubicin
- Carmustine
- Dactinomycin

### Irritants
- Bendamustine
- Carboplatin
- Etoposide
- Irinotecan
- Temsirolimus
- Teniposide
- Irinotecan
- Temsirolimus
- Teniposide
- Irinotecan
- Temsirolimus
- Teniposide
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- Teniposide

### Inflammants
- Fluorouracil (5FU)
- Methotrexate
- Raltitrexed
- Irinotecan
- Temsirolimus
- Teniposide
- Irinotecan
- Temsirolimus
- Teniposide
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- Temsirolimus
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### Neutrals
- Asparaginase
- Bevacizumab
- Bleomycin
- Cetuximab
- Cyclophosphamide
- Cytarabine
- Eribulin
- Fludarabine
- Gemcitabine
- Ifosfamide
- Melphalan
- Pemetrexed
- Pentostatin
- Rituximab
- Thiotepa
- Trastuzumab

*(due to the vesicant nature a central line is strongly recommended in the SPC)*

However any chemotherapy drug has the potential to cause significant symptoms or harm if the volume or concentration of the drug that extravasates is high. European Oncology Nursing Society (2007)

**IF AN EXTRAVASATION OCCURS WITH A DRUG NOT LISTED ABOVE PLEASE CONTACT PHARMACY ASEPTIC SUITE FOR ADVICE**
Identification of Risk Factors

Patient factors
- Age: very young and elderly patients tend to have small mobile veins with friable skin.
- Cancer patients may have additional risk due to:
- Due to multiple cannulations for chemotherapy veins maybe hard or sclerosed.
- Lymphoedema
- Previous treatment e.g. mastectomy.
- Patients with long term side effects from treatment e.g. peripheral neuropathy
- Previous extravasation injury site
- Multiple investigations e.g. blood tests
- Obstructed vena cava (elevated venous pressure can cause leakage).
- Unconscious, sedated, confused patients or patients with communication problems who may be unable to report stinging or discomfort around the cannula site or decreased sensation.
- Patients suffering from co-morbidities which may lead to decreased sensation or poor circulation e.g. diabetes, cerebral vascular accidents
- Obesity.
- Concurrent medication i.e. analgesics, anticoagulants, anti-fibrinolytics, vasodilators, hormone therapy, steroids, diuretics, anti-histamines, intravenous antibiotics
- Communication difficulties

Cannulation and Infusion Procedure Factors
- Inferior choice of site for cannulation may increase the risk of a large volume extravasation or may impact on the severity of the injury
- Difficult or multiple attempts at cannulation increase the risk of a subsequent extravasation.
- Administration of chemotherapy by untrained or inexperienced staff increases the risk of extravasation.
- Steel cannulae must not be used for the administration of chemotherapy
- The size of cannula
- The utilisation of a pre-existing cannula
- The classification of chemotherapy drug

Prevention of Extravasation
The following key areas have been identified in minimising the risk of extravasation

Training
Only staff who have completed appropriate training should administer chemotherapy unsupervised. Staff should attend regular chemotherapy updates (either internally or externally facilitated) ideally annually and as a minimum every two years. Competency to administer chemotherapy must be checked annually and should include the demonstration of knowledge regarding
- Assessment of venous access
- Venous access devices
- Administration of chemotherapy
- Prevention, recognition and management of extravasation
- Management of chemotherapy related complications

Selection of site for cannulation
- The choice of site is paramount when attempting cannulation for chemotherapy. Cannulating over joints or the anticubital fossa should be avoided as tissue damage due to extravasation may have serious consequences as there is little soft tissue for the protection of underlying nerves and tissues. (Allwood & Stanley 2002; Hayden & Goodman, 2005; Weinstein, 2007; Dougherty and Lamb, 2008; RCN 2010).
• When choosing a vein to site the cannula a large straight, firm, pliable vein which has not been utilised within the previous 24 hours would be the ideal choice
• However if the most suitable vein for cannulation has been utilised within the last 24 hours for either cannulation or phlebotomy, any attempt should be higher (closer to the patient’s heart).
• If cannulation attempt fails then further cannulation attempts must be above the previous site.

<table>
<thead>
<tr>
<th>Criteria for vein selection</th>
<th>Appropriate choice of venepuncture site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most Desirable</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ideal vein / best location</strong> large, soft, resilient veins in forearm</td>
<td>Forearm</td>
</tr>
<tr>
<td><strong>Ideal vein / less desirable location</strong> large, soft, resilient veins in hand/antecubital fossa</td>
<td>Hand</td>
</tr>
<tr>
<td><strong>Satisfactory vein / best location</strong> small, thin veins in forearm</td>
<td>Forearm</td>
</tr>
<tr>
<td><strong>Satisfactory vein / undesirable location</strong> small, thin veins in hand; veins in forearm not palpable or visible</td>
<td>Hand</td>
</tr>
<tr>
<td><strong>Unsatisfactory vein / undesirable location</strong> small, fragile veins, which easily rupture in forearm/hand</td>
<td>Consider central venous line</td>
</tr>
</tbody>
</table>
Guideline for the management of extravasation

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Vein selection

Least desirable

Unsatisfactory vein / undesirable location

veins in forearm/hand not palpable or visible

Consider central venous line

(Hughes 1984)

Choice of equipment

- A new cannula ideally should be placed prior to the administration of chemotherapy. There is an increased risk of extravasation if a previously placed cannula is utilised.
- It is recommended that the smallest gauge cannula is placed in the biggest vein possible.
- Steel winged infusion devices are associated with a higher incidence of extravasation therefore in no circumstances should a metal butterfly needle be utilised to for the administration of chemotherapy.
- The vascular access device should be secured utilising a clear dressing that enables visibility whilst maintaining adequate fixation.
- Infusion lines must be secured effectively, however never cover the line with a bandage as the insertion point must be visible at all times.

Patient Education

- Communication with the patient plays a vital role in the recognition of extravasation.
- Patients should be informed of the importance of reporting immediately any change in sensation, stinging or burning during the administration of chemotherapy.
- For patients with communication difficulties who rely on carers or interpreters, it is important to establish that they understand the significance of reporting symptoms immediately.

Administration

- Consideration should be given to the use of a central venous access device (CVAD) in certain situations i.e. regimes with prolonged infusion of vesicant agents, if the patient has previously had an extravasation or for certain agents an example being Trabectedin where the summary of product characteristics recommends a CVAD.
- Ideally a new peripheral cannula should be sited immediately prior to chemotherapy administration.
- Only in exceptional circumstances should a practitioner who is going to administer vesicants or irritants utilise a cannula placed by another practitioner.
- If the practitioner has any doubts in relation to the vascular access device the patient should be re cannulated proximal to first attempt.
- Ideally a practitioner will only attempt to cannulate a patient twice before handing over to another practitioner.
Venous access should be assessed and tested immediately prior to and frequently throughout administration of any cytotoxic drugs, checking for backflow, no resistance on syringe plunger on administration and acceptance of free flowing compatible infusion fluid.

If multiple drugs are prescribed within the chemotherapy protocol, ideally vesicants should be administered first when vein integrity is at its best. However there are notable exceptions where it is clinically indicated within the protocol that a non vesicant should be given first.

If a non vesicant is administered first for clinical reasons the patency of the cannula should be reassessed prior to administration of vesicants. If there are doubts regarding the integrity of the cannula or the vein the patient should be recannulated.

When administering bolus vesicant agents they should be administered through the side arm of a fast flowing compatible fluid drip continually assessing for signs of extravasation.

The delivery of chemotherapy irrespective of the agent being vesicant or not, is about the individual patient and the clinical assessment any practitioner makes at the time of the administration and will show huge inter and intra patient variability. The administration of chemotherapy needs to be guided by the skill and clinical judgment of the practitioner in the specific and individual circumstances of that administration.

It is known that certain pharmacological and formulation issues such as pH make a difference; volume and temperature are also important, larger volumes will require slower administration and the greater the temperature gradient between the administered drug and physiological 36.8 the greater the degree of ‘venous shock’ and consequential shut down and risk of extravasation.

Between each intravenous drug administration and on the completion of treatment the cannula should be flushed with compatible fluid.

A number of regimens may now require patients to receive infusional vesicant agents, Patients receiving vesicant agents in this way should be closely monitored for signs of extravasation as there may be a theoretical increased risk of a larger volume extravasation.

In particular the Vinca Alkaloids which in response to the NPSA alert RRR004 (NPSA 2008) should only be supplied in the form of minibags for infusion.

The prescribed dose of Vinca Alkaloids should be supplied ready to administer in a 50ml minibag of sodium chloride 0.9% (for some brands of Vinorelbine glucose 5% solution for injection may be used instead of sodium chloride 0.9%).

All vinca alkaloid doses should be labelled 'For Intravenous Use Only - Fatal If Administered by Other Routes'.

There should be use of colour and design on the label, outer packaging and delivery bags to further differentiate minibags containing vinca alkaloids from other minibag infusions. (NPSA/2008/RRR004).

The vinca minibag should be infused intravenously over 5 -10 minutes.

Patients receiving peripheral intravenous infusions of vesicant drugs must not be allowed to leave the clinical area, and MUST be observed at all times.

Night time infusions of potentially vesicant drugs should not be normal practice and should be avoided unless urgent and clinically indicated.
Recognition of extravasation
The early recognition and diagnosis of extravasation is critical as delays in the recognition and management of a vesicant extravasation increase the likelihood of tissue damage and necrosis (McCaffrey Boyle D, Engelking C 1995, EONS 2007). The awareness and responsiveness to signs and symptoms is the most effective way to recognise and detect extravasation. If an extravasation is suspected it is important that a correct diagnosis is established seeking a second opinion is always warranted if in any doubt.

Patient reporting
Patients must be informed of the potential risk of extravasation and the importance of reporting any symptoms below irrespective of how insignificant they may be
- Pain
- Change in sensation
- Burning
- Stinging
- Discomfort

Patients must be informed that these symptoms may not be an extravasation, however that a definitive diagnosis will need to be established.

Visual Assessment
Visual signs, while by no means exclusive to extravasation, do provide useful confirmation for patient reporting of symptoms in suspected extravasation. The common signs, occurring at or around the site of the cannula – or, in the case of central line around the Central Venous Access Device and the surrounding area –include:
- Early symptoms
  - Swelling/oedema
  - Redness/erythema
- Later symptoms
  - Inflammation
  - Induration
  - Blistering

Importantly, many of these symptoms do not occur immediately upon infusion, induration and blistering, in particular, tend to appear later in the extravasation process. Therefore, careful monitoring of the site should continue during the infusion time and for some time following an infusion. Patients should be informed of the importance of reporting any pain, swelling, inflammation, blistering around the infusion site that occurs when at home. (EONS 2007).

Warning signs related to the Vascular Access Device
In addition to the patient reporting of symptoms and visual assessment, the following may support a diagnosis of extravasation
Signs of extravasation, in relation to the cannula, include:
- Increased resistance when administering IV drugs
- Slow or sluggish infusion
- Change in infusion flow
- Lack or loss of blood return from the cannula
- Leakage from around the cannula site

It is important to note that all signs and symptoms may not occur instantaneously and if the practitioner has any concerns then the administration should be stopped immediately until extravasation is excluded. If a definitive diagnosis cannot be established however other potential diagnoses have been excluded then the extravasation procedure should be instigated.
**Distinguishing between Extravasation and other conditions**

A definitive diagnosis can be difficult to establish and requires expert clinical judgement. However a definitive diagnosis enables the initiation of appropriate interventions and management strategies at the earliest possibility opportunity.

The following table distinguishes between other possible conditions that resemble extravasation.

<table>
<thead>
<tr>
<th></th>
<th>Presenting Symptoms</th>
<th>Colouration</th>
<th>Timing</th>
<th>Swelling</th>
<th>Blood return</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flare Reaction</strong></td>
<td>Itchy blotches or hives; Pain &amp; burning uncommon</td>
<td>Raised red streak, blotches or ‘hive-like’ erythema along the vessel; Diffuse or irregular pattern</td>
<td>Usually appears suddenly and dissipates within 30-90 minutes</td>
<td>Unlikely</td>
<td>Usually but not always</td>
</tr>
<tr>
<td><strong>Vessel Irritation</strong></td>
<td>Aching and tightness</td>
<td>Erythema or dark discolouration along the vessel</td>
<td>Usually appears within minutes after injection. Colouration may only appear later in the process</td>
<td>Unlikely</td>
<td>Usually but not always</td>
</tr>
<tr>
<td><strong>Venous Shock</strong></td>
<td>Muscular wall of the blood vessel in spasm</td>
<td>Erythema around area of needle or around the venepuncture site</td>
<td>Usually appears straight after the injection</td>
<td>Often absent</td>
<td></td>
</tr>
<tr>
<td><strong>Extravasation</strong></td>
<td>Pain and burning are common at injection site; Stinging may occur during infusion</td>
<td>Erythema around area of needle or around the venepuncture site</td>
<td>Some symptoms start to appear straight after the injection; Symptoms endure</td>
<td>Occurs often Does not dissipate for several days</td>
<td>Usually absent or sluggish</td>
</tr>
</tbody>
</table>

EONS (2007)
Management of Extravasation
The management of an extravasation is dependent upon a number of contributing factors:

- The drug involved
- The volume extravasated
- The site of the extravasation

The early initiation of treatment reduces the potential for tissue damage and necrosis and therefore is a critical part in the management of extravasation. However in some cases an extravasation injury may not become apparent until a number of days or weeks later.

Extravasation is an oncology emergency and treatment should be initiated as soon as extravasation is suspected.

It is now acknowledged that there are three tiers of management of an extravasation:

- Basic management of extravasation (1st line)
- Decide on appropriate treatment based on cytotoxic involved (2nd line)
- Specific management instructions (3rd line)

If an extravasation is suspected the most senior nurse should co-ordinate the management of the extravasation. A doctor should be informed of the incident immediately; in the case of vesicants or an extravasation via a CVAD a consultant should be informed.

Basic Management of Extravasation- The pathway for first line management is as follows:-
Irrespective of the nature of the drug the initial response to a suspected extravasation is the same. The initial aim is to minimise the volume of extravasated cytotoxic into the surrounding tissues.

IF AN EXTRAVASATION IS SUSPECTED THE MOST SENIOR NURSE SHOULD CO-ORDINATE THE MANAGEMENT OF THE EXTRAVASATION.
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**Guideline for the management of extravasation**

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Pathway for 2nd line management

The subsequent management of a suspected extravasation is determined by the cytotoxic drug involved. There are two specific pathways for the 2nd line management of extravasation, localise and neutralise (cold packs) and disperse and dilute (warm packs). For some cytotoxic’s there is currently no further specific action other than basic management and symptom management required, however the patient should be given a follow up appointment and informed of the importance of contacting the chemotherapy team if further concerns arise.

The following table indicates the pathway required for individual cytotoxic agents.

| Step 1 | • Stop the infusion immediately  
• Do not remove the cannula/central venous access device (CVAD) |
|---|---|
| Step 2 | • Inform and reassure the patient what is happening  
• Request a member of staff to collect extravasation kit and bring to patient |
| Step 3 | • Disconnect the infusion from the cannula/CVAD |
| Step 4 | • Try to aspirate as much as possible from the cannula/CVAD with a 10ml syringe  
• Do not apply direct pressure to the suspected extravasation site |
| Step 5 | • Mark the affected area with a waterproof pen and with patient consent if possible take digital image |
| Step 6 | • Remove the cannula/needle. Do not remove CVAD |
| Step 7 | • Elevate limb  
• Inform haematology/oncology medical team, contact the Haematology/Oncology consultant immediately if a CVAD or vesicant is involved in the extravasation |
| Step 8 | • Administer pain relief if required |
| Step 9 | • Follow the 2nd line management pathway  
• Consider 3rd line management |

For suspected extravasation in central venous access device the haematology/oncology consultant should be informed immediately and steps 1-5 should be followed, a discussion with and consideration of a subsequent referral to specialist plastic surgical team needs to be undertaken before a decision regarding central line removal.
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Cold/Warm pack</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane</td>
<td>Vescant</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>Vescant</td>
<td>Cold</td>
<td>Hydrocortisone cream</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Neutral</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>Irritant</td>
<td>Cold</td>
<td>Hydrocortisone cream</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Neutral</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Neutral</td>
<td>None</td>
<td>No antidote</td>
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<td>Cabazitaxel</td>
<td>Vescant</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
</tr>
<tr>
<td>Carboplatin*</td>
<td>Irritant</td>
<td>See specific advice*</td>
<td>See specific advice*</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Vescant</td>
<td>Cold</td>
<td>Hydrocortisone cream</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Neutral</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>Exfoliant</td>
<td>See specific advice*</td>
<td>See specific advice*</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Neutral</td>
<td>None</td>
<td>No antidote</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Neutral</td>
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<td>No antidote</td>
</tr>
<tr>
<td>Cytarabine</td>
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<td>No antidote</td>
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<td>Daclarbazine</td>
<td>Vescant</td>
<td>Cold</td>
<td>Hydrocortisone cream</td>
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<tr>
<td>Dactinomycin</td>
<td>Vescant</td>
<td>Cold</td>
<td>DMSO</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Vescant</td>
<td>Cold</td>
<td>DMSO or Savene</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Await Urgent Medical decision regarding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>antidote</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Exfoliant</td>
<td>Warm</td>
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<td>No antidote</td>
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<td>Inflammitant</td>
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<td>Hydrocortisone cream</td>
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<tr>
<td>Gemcitabine</td>
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<td>No antidote</td>
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<td>Vinorelbine</td>
<td>Vescant</td>
<td>Warm</td>
<td>Consider Hyaluronidase</td>
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Specific advice for Carboplatin and Cisplatin
If treatment is administered within 24 hours then a warm pack and consider Hyaluronidase would be the treatment of choice, however if the injury is not treated within 24 hours a cold pack and hydrocortisone cream would then be the appropriate management.

IF AN EXTRAVASATION OCCURS WITH A DRUG NOT LISTED ABOVE PLEASE CONTACT PHARMACY ASEPTIC SUITE FOR ADVICE

2\textsuperscript{nd} line pathway- Disperse and Dilute Pathway (continues from Step 9 of initial management)
The Disperse and dilute 2\textsuperscript{nd} line pathway utilises warm compresses to promote vasodilation and encourage blood flow in the tissues therefore spreading the extravasated agent. Hyaluronidase may be utilised with the aim of promoting drug diffusion and enhancing drug absorption.
2nd line pathway-Localise and Neutralise Pathway (continues from Step 9 of initial management)

The localise and neutralise pathway utilises cold compresses to limit the spread of the extravasated agent. It is proposed that the cellular uptake of the agent into the tissues is reduced when cold compresses are utilised. The cold compresses also may reduce local discomfort.

There are a number of antidotes available for certain cytotoxic agents and these are drug/group specific, these should be considered for 3rd line management to reduce the potential for severe tissue damage or injury.
Step 10
- Localise
- Apply a cold pack to the affected area for 20 minutes 4 times daily for 1-2 days ensuring that the icepack does not come into direct contact with the skin.

Step 11
- Neutralise the drug by using the specific antidote (3rd line pathway if available) **ON HEMATOLOGY/ONCOLOGY MEDICAL ADVICE**
- Only certain cytotoxics have specific antidotes
- If no antidote this step is omitted

Step 12
- Elevate the limb
- Consider the utilisation of topical or systemic analgesia if required

Step 13
- Document the incident on trust documentation and on green card

Step 14
- Arrange follow up for patient

3rd line Pathway for specific cytotoxic agents
Following commencement of the 2nd line management pathways, clinicians should consider the utilisation of antidotes where available. These antidotes when utilised appropriately may help to prevent progression to ulceration and severe tissue damage. This decision will be based on a holistic assessment of the individual patient, their treatment protocol, the suspected extravasated drug, their co-morbidities and concurrent medications. The evidence to support the utilisation of antidotes is often inconclusive and any decision to utilise these antidotes should be carefully considered. It is the responsibility of the treating clinician to consider and refer to plastic surgeon if appropriate.
### Extravasated Drug

<table>
<thead>
<tr>
<th>Extravasated Drug</th>
<th>Suggested antidote</th>
<th>Level of evidence</th>
<th>Advice</th>
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<tr>
<td>Anthracyclines</td>
<td>Savene (Dexrazoxane) The only licensed antidote. Savene neutralises anthracyclines</td>
<td>Efficacy in biopsy confirmed anthracycline extravasation has been confirmed in clinical trials</td>
<td>3 day course of treatment Day 1 (within 6 hours of extravasation) 1000mg/m². Day 2 1000mg/m². Day 3 500mg/m².</td>
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<tr>
<td>Anthracyclines</td>
<td>Topical DMSO (99%) It is proposed this prevents ulceration by its property of scavenging free radicals</td>
<td>Suggested as a possible antidote in many literature sources.</td>
<td>Apply locally as soon as possible. Repeat every 8 hours for 7 days stop if blistering occurs</td>
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<tr>
<td>Mitomycin C</td>
<td>Topical DMSO (99%) It is proposed this prevents ulceration by its property of scavenging free radicals</td>
<td>Suggested as a possible antidote in many literature sources.</td>
<td>Apply locally as soon as possible. Repeat every 8 hours for 7 days stop if blistering occurs</td>
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<tr>
<td>Vinca alkaloids</td>
<td>Hyaluronidase Breaks down hyaluronic acid (&quot;cement&quot;) in connective/soft tissue, allowing for dispersion of the extravasated drug, thereby reducing the local concentration of the damaging agent and increasing its rate of absorption</td>
<td>Suggested as a possible antidote in many literature sources.</td>
<td>150–1500 IU subcutaneously around the area of extravasation</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Hyaluronidase Breaks down hyaluronic acid (&quot;cement&quot;) in connective/soft tissue, allowing for dispersion of the</td>
<td>Suggested as a possible antidote in many literature sources.</td>
<td>150–1500 IU subcutaneously around the area of extravasation</td>
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**Guideline for the management of extravasation**

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extravasated drug, thereby reducing the local concentration of the damaging agent and increasing its rate of absorption

Schrijvers (2003)

Within WAHT, If DMSO 99% is not available, the 50% solution will be used as an alternative

Appendix 2, 3, 4 detail the specific individual drug management instructions for Savene, DMSO and Hyaluronidase.

Follow Up
- All patients must have a review of their extravasation injury within 1 week, this appointment must be arranged prior to the patient leaving clinic
- Advise the patient of the importance of contacting the 24 hour helpline if there is any deterioration in the affected limb

Documentation
- Ensure all extravasations are reported on the Datix system to enable monitoring and review of incidents.
- All incidents should be reported to the National Extravasation service either via the green cards or online at www.extravasation.org.uk
- Ensure that the extravasation injury is recorded in line with the NMC standards for record keeping. The suggested documentary requirements for an extravasation injury are detailed in Appendix 5

Monitoring Tool
Yearly audit to monitor the prevalence and management of extravasation.

<table>
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<th>STANDARDS</th>
<th>%</th>
<th>CLINICAL EXCEPTIONS</th>
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<td>All patients who are suspected of having an extravasation injury will have the incident reported on Datix and green card monitoring systems</td>
<td>100%</td>
<td>None</td>
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</table>
Guideline for the management of extravasation

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It is the responsibility of every individual to check that this is the latest version/copy of this document.

References

- Spepharm: Healthcare professionals’ clinical guide: Management of Anthracycline Extravasation with Savene® (dexrazoxane)
- Summary of product characteristics: Savene accessed November 2010.
It is the responsibility of every individual to check that this is the latest version/copy of this document.

Acknowledgements
National Extravasation Information Service. [www.extravasation.org.uk](http://www.extravasation.org.uk) accessed November 2010
Local, and network guidelines were reviewed in the development of this document.
Appendix 1

Extravasation Kit

- Copy of extravasation guideline (also available on the intranet)
- Green cards for reporting extravasation injury (can also be reported at www.extravasation.co.uk)
- 10ml syringes
- Green needles, orange needles
- Water for injection
- Alcohol wipes
- Sterile gauze and cotton wool
- Cold and hot packs (available within chemotherapy units)
- Hyaluronidase 1500 units x 2 (administration instructions appendix 4 in extravasation guideline)
- DMSO (administration instructions appendix 3 in extravasation guideline)
- Hydrocortisone 1% cream-labelled with instructions for use to reduce local trauma and irritation
- Non-occlusive dressing
- Savene Kit available in aseptic suite (administration instructions appendix 2 in extravasation guideline)
Appendix 2

Administering Savene (Dexrazoxane)
THE DECISION TO UTILISE EITHER SAVENE OR DMSO FOR AN ANTHRACYCLINE EXTRAVASATION MUST BE UNDERTAKEN BY A MEDIC BASED ON AN ASSESSMENT OF THE INDIVIDUAL’S COMORBIDITIES AND CONCURRENT MEDICATIONS

INDICATION
Savene is indicated for the treatment of extravasation by one of the following anthracycline agents: Doxorubicin, Epirubicin, Idarubicin and Daunorubicin.

DMSO must not be used concurrently

Steps for administration.

1. Follow 1st two steps of localise and neutralise 2nd line pathway for extravasation (pg 19)
2. The indicated dose should be administered as an intravenous infusion over 1-2 hours into a large vein in an extremity / area other than the one affected by the extravasation. The first infusion should be initiated as soon as possible and within the first six hours after the incident.
3. Cooling procedures such as ice packs should have been removed from the area at least 15 minutes prior to Savene administration in order to allow sufficient blood flow. DMSO should not be used concurrently.
4. Before infusion, Savene powder must be reconstituted with 25 ml sterile water to give a concentrate of 20 mg dexrazoxane per ml sterile water.
5. After reconstitution, the concentrate should then be further diluted in the bag with 500 ml Savene diluent.
6. Savene will be reconstituted during normal working hours within the aseptic suite at Worcester (where the Savene kit will be stored).
7. Outside working hour’s pharmacy cannot guarantee that an on call pharmacist with the skills required will be available.
8. Only in this situation will the Savene be reconstituted on Laurel 3 utilising the phaseal device by staff that have undergone training in reconstitution. The on call pharmacist will ensure that the kit is made available to staff on Laurel 3 in a timely manner.
9. Savene should be given once daily for three consecutive days. The patient will need to be recannulated for each infusion as Savene is classified as a cytotoxic agent.
10. The recommended dose according is:
   a) Day 1: 1000mg/m²
   b) Day 2: 1000mg/m²
   c) Day 3: 500mg/m²
11. For patients with a body surface area of more than 2 m² the single dose should not exceed 2000 mg.
12. Treatment on Day 2 and Day 3 should start at the same hour (+/- 3 hours) as on the first day.
13. The Savene kit contains 10 vials of Savene powder each containing 500mg.
Dexrazoxane and 3 bags of Savene diluent
14. The kit must be stored at less than 25°C
15. After reconstitution Savene should be stored for no longer than 4 hours at
   • 2-8°C

For full prescribing information, contraindications, precautions and warnings please refer to summary of product characteristics and spepharm health professionals’ guide
Pathway for patients requiring Savene at Worcestershire Acute Hospitals NHS Trust.

**Step 1**
• Suspected extravasation of **epirubicin, doxorubicin, idarubicin, daunorubicin**

**Step 2**
• Basic management of extravasation initiated and completed

**Step 3**
• 2nd line pathway localise and neutralise commenced

**Step 4**
• **MEDICAL DECISION** to utilise savene based on individual's co-morbidities and concurrent medications
  • If a decision to utilise Savene, DMSO must not be used concurrently

**Step 5**
• If extravasation has occurred at either Kidderminster or Redditch the patient will be required to transfer to Worcester
  • Patient informed of treatment options and requirement to transfer to Worcester for Savene treatment

**Step 6**
• Clinician to prescribe savene based on patients height and weight
  • If outside normal working hours on call pharmacist at Worcester contacted
  • Prescription faxed to aseptic suite at Worcester supported by telephone referral to pharmacy and treatment area

**Step 7**
• Aseptic suite at Worcester to reconstitute Savene
  • If outside working hours on-call pharmacist will (if appropriately trained) reconstitute Savene in aseptic suite. If no appropriately trained on call pharmacy staff available, on call pharmacist will deliver to Laurel 3 for staff to reconstitute Savene (who have been trained) utilising the Phaseal device

**Step 8**
• If transferring from Redditch or Kidderminster organise emergency ambulance for transfer

**Step 9**
• Patient transferred to Rowan Suite during normal working hours and Laurel 3 if outside normal working hours or predicted time of completion outside normal working hours

**Step 10**
• Patient cannulated and first infusion of Savene commenced
  • Following each infusion of Savene the cannula will need to be removed and resited when the patient attends for subsequent treatment

Steps 1-10 of pathway must be completed within 6 hours.
Appendix 3

Administering Dimethylsulfoxide (DMSO)

THE DECISION TO UTILISE EITHER SAVENE OR DMSO FOR AN ANTHRACYCLINE EXTRAVASATION MUST BE UNDERTAKEN BY A MEDIC BASED ON AN ASSESSMENT OF THE INDIVIDUAL'S CO-MORBIDITIES AND CONCURRENT MEDICATIONS.

Dimethylsulfoxide (DMSO 50%) is an unlicensed option for the treatment of extravasation with anthracyclines including Doxorubicin, Idarubicin, Epirubicin, Daunorubicin; it can also be used to treat extravasation with Mitomycin C, Mitoxantrone, Dactinomycin, Liposomal Daunorubicin and Liposomal Doxorubicin.

As this is an unlicensed indication patient details must be recorded when DMSO is utilised

Steps for administration:

1. Follow steps for localisation and neutralisation of extravasation (page 19)
2. Draw around the area with indelible pen.
3. Put gloves on
4. Carefully apply a thin layer of DMSO topically to the marked area avoiding contact with unaffected areas
5. Allow it to dry,
6. This should be applied ideally within 10 – 25 minutes,
7. Check for erythema caused by DMSO.
8. Repeat administration of DMSO every 6 hours for 7 days
9. Advise patient to stop using DMSO and contact chemotherapy unit if blistering occurs

Note:
Please refer to DMSO prescribing information for a full list of contraindications, precautions and warnings.

(EONS 2007)
Appendix 4

Administering Hyaluronidase

Hyaluronidase has been suggested as a possible antidote for some extravasations in many literature sources. It works by breaking down hyaluronic acid (“cement”) in connective/soft tissue, allowing for dispersion of the extravasated drug, thereby reducing the local concentration of the damaging agent and increasing its rate of absorption. (Schrijvers 2003)

Steps for administration:

1) Follow steps for dispersion and dilution of extravasation (page 14)

2) Administration of hyaluronidase should begin within 1 hour of extravasation for best results.

3) Dilute 150 – 1500 IU of hyaluronidase in 1 ml of sterile water,

4) Use 25 or 27 gauge needle and change after each injection,

5) Subcutaneously (or intradermally) inject 1 ml (150 IU) of hyaluronidase as 5 separate 0.2 ml injections around the periphery of extravasation site.

Note: Please refer to hyaluronidase prescribing information for a full list of contraindications, precautions and warnings.

(EONS 2007)
Appendix 5

Documentation Requirements

Each incident of extravasation must be thoroughly documented and reported. (Dougherty & Lister 2008)

Documentation serves several purposes:

- To provide an accurate account of what happened (in the event that there is litigation)
- To protect the healthcare professionals involved (showing they followed procedure)
- To gather information on extravasations, how and when they occurs – for audit purposes
- Highlight any possible deficits in practice which require review

Following an extravasation, the following details should be documented: (Dougherty & Lister 2008, Polovich et al 2006)

- Patient name and number
- Clinical area
- Date and time of extravasation
- Name of drug which has extravasated
- Signs and symptoms
  - Colour of surrounding skin
  - Size of extravasation
- Description of the IV access
  - Venepuncture site
  - Size and position of cannula
  - Number of attempts at obtaining venous access and positions
  - Drugs administered and the sequence
  - Drug administration technique (bolus or infusion)
  - Blood return
- Extravasation area
  - Approximate amount of the drug extravasated
  - Photograph of extravasated area
  - Size (diameter, length and width) of extravasation area
  - Appearance of extravasation area
- Step-by-step management with date and time of each step performed and medical notification
  - Aspiration possible (including amount) or not, location (venous and/or subcutaneous) and amount
  - Cold/heat
  - Antidote
  - Referral details (if any)
- Patient’s complaints, comments, statements
- Indication that patient’s information sheet given to patient
- Follow-up instructions given (to patient, nurse, physician, etc.)
- Names of all professionals involved in the patient management
- Signature of nurse

All follow up care should be documented in the notes and all visual assessments should be recorded.
Appendix 6

Patient Information

What is extravasation?
Extravasation is a term used when a small amount of a drug has accidently leaked from the vein into a surrounding tissues. You may have noticed pain; stinging, swelling or other changes to the skin at the site of drug administration, or the nurse may have noticed that the drug was not flowing in easily.
The extent of the injury depends on the chemotherapy involved and can vary from a mild reaction with irritation and inflammation to in some cases the drug which has leaked causing local pain, stiffness and tissue damage.

Why did this happen?
Extravasation is a rare but known complication of intravenous chemotherapy. Despite all possible measures to prevent this happening sometimes it is impossible. The important thing is that it has been detected and treated.

What treatment have I received to prevent tissue damage?
The nurse has treated the extravasation with the recommended treatment for the particular drug involved. Although this treatment may help to minimise the chance of further problems occurring we ask that you monitor the area daily.

Checking the area
Once a day, check the area for the following:
• Has the area changed colour or increased in redness?
• Is the area blistering, peeling or flaking?
• Is the area more uncomfortable?
• Is the pain making it difficult for you to exercise the arm or hand?

What else do I need to do?
Follow the specific instructions written in the box below by the nurse

• Gently exercise the affected arm or hand.
• Take mild painkillers if required.
• Do not apply any other lotions, creams or ointments unless you have been instructed to do so by a doctor or nurse.
• Do not expose the area to strong sunlight.
• Avoid wearing tight clothing around the affected area.
• Protect the affected area when bathing (or having a shower) so that it does not get wet.

When should I contact you?
If you answered YES to any of the questions in the checklist above, or if you have any other concerns, then you must contact someone at this hospital who is experienced in extravasation.
Contact Telephone Number …………………………………..
**Contribution List**

**Key individuals involved in developing the document**

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<tbody>
<tr>
<td>Sue Sharp</td>
<td>Macmillan Chemotherapy/ Radiotherapy Project Nurse</td>
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<tr>
<td>Lynne Colbourne</td>
<td>Advanced Nurse Practitioner for the Emergency Care Pathway</td>
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<tr>
<td>Fay Lanham</td>
<td>Oncology CNS</td>
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<tr>
<td>Peter James</td>
<td>Rowan Suite Manager</td>
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<tr>
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<td>Haematology CNS</td>
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<td>Ms T Thomas</td>
<td>CNS Haematology</td>
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<td>Rachel Desogus</td>
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<tr>
<td>Glenis Adams</td>
<td>Matron Cancer Services and Medicine</td>
</tr>
<tr>
<td>Anne Sullivan</td>
<td>Lead Cancer Nurse/Cancer Manager</td>
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<tr>
<td>Shafeek Salim</td>
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**Guideline for the management of extravasation**

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