Extravasation guidelines 2007

Guidelines

Implementation Toolkit

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Extravasation guidelines 2007

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Key points to understand from the extravasation guidelines

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Introduction

With over 100,000 doses of chemotherapy and in excess of 1,000,000 intravenous (IV) infusions given every day around the world, keeping adverse events and complications of these procedures to a minimum is important both for the patients receiving them and the healthcare systems in which they take place.

Extravasation is a serious condition that warrants special attention from the healthcare professionals involved in administering intravenous medications. This educational module summarises and explains the most recent literature and recommendations on extravasation in the clinical setting – from prevention and recognition to possible treatment with antidotes. It also provides an outline of the pivotal role that nurses play in the patient management process.

The scope of this document is to describe and explain the prevention, recognition and management of extravasation in general terms. More detailed descriptions of techniques for proper cannulation or phlebotomy (an important skill for the prevention of extravasation) will not be dealt with in this guideline.

Overall Goal

The overall goal of these guidelines is to help nurses understand and recognise extravasation, and improve the prevention and overall management of extravasations in cancer patients.

Specific Targets and Aims

The targets and aims of this module are to:

- Increase nurses' knowledge of specific elements of extravasation:
  - Causes and risk factors for extravasation
  - Features and symptoms of extravasation
  - Differences vs. flare and other reactions
  - Consequences of extravasation
  - Prevention measures
  - The use of antidotes in treating extravasation
- Encourage successful management of extravasation
- Update and inform nurses of the current standards from different guidelines and protocols
- Encourage adoption of procedures for extravasation that fit with the current guidelines

The Nurse's Role

Nurses are among the best placed professionals to recognise and deal with extravasation in the clinical setting. The nurses who routinely provide cancer therapies intravenously (either peripherally or through central venous access devices (CVADs) are particularly important in the ongoing management of this possibly serious complication of therapy.

Nurses have a key role to play in identification and management of extravasation, and, of course, in preventing it. From maintaining a high standard of care in the delivery of IV drugs to managing the treatment strategy for extravasation, they have many important duties in this area.

Nurses represent an important link for ensuring that extravasation is prevented, diagnosed and managed where possible. Their role in providing information and providing ongoing support for patients relating to cancer therapy (and the need to be vigilant for any symptoms) is critical in cutting the incidence of extravasation.

This module will discuss the role of the nurse in extravasation management and highlight information and issues that will assist nurses to perform these roles more efficiently.

What is extravasation?

In a general sense, extravasation refers to the process by which one substance (e.g., fluid, drug) leaks into the surrounding tissue.[1] In terms of cancer therapy, extravasation is defined as the accidental leakage from its intended compartment (the vein) into the surrounding tissue.[2] Usually, this occurs when intravenous (IV) medication passes from the blood vessel into the tissue around the blood vessels and beyond.[1–4]

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.[4]

Types of extravasation

Types of extravasation

Extravasation can be classified according to the reaction that is caused by the substance passing into the surrounding tissue. Many different drugs have been classified according to the type of reaction they cause; however, for the purpose of this discussion, we will refer only to cancer therapies. It should be noted, however, that cancer therapies are not the only drugs that cause damage when extravasated, and non-cancer therapies (e.g., aminophylline, calcium solutions, hypertonic glucose, phenytoin, total parenteral nutrition, X-ray contrast media) can be equally as destructive.[5]

Cancer drugs can be grouped into 3 broad categories, based on their potential to cause tissue damage upon extravasation:[3]

- Non-vesicants
- Irritants
- Vesicants

Non-vesicants do not cause ulceration. In fact, if they are extravasated, they rarely produce an acute reaction or progress to necrosis.[3] Irritants, on the other hand, do tend to cause pain at, and around the injection site, and along the vein. They may or may not also cause inflammation. Some irritants do also have the potential to cause ulceration, but only in the case that a very large amount of the drug is extravasated into the tissue.[3]

Vesicants are drugs that have the potential to cause blistering and ulceration and which when left untreated, can lead to the more serious side effects of extravasation such as tissue destruction and necrosis.[3] These drugs can be sub-classified according to the mechanism by which they cause damage, which is also important since it affects the management strategy.[3]

- DNA-binding: These drugs are absorbed locally and enter the cells, bind to nucleic acids (i.e., DNA) and precipitate the death of the cell. Following cell death these agents can be re-released to destroy non-cancer cells. They can be divided into 3 categories:[3]
  - Anthracyclines
  - Alkylating agents
  - Others
- Non-DNA-binding: These drugs initiate cancer cell death by mechanisms other than binding DNA. They can be divided into 2 groups:[3]
  - Vinca alkaloids
  - Taxanes

For a comprehensive list of vesicants (including all subcategories), irritants and non-vesicants please refer to Appendix 1.

When does extravasation occur?

In an ideal situation, extravasation of vesicant cancer therapies would never occur. Despite the many precautionary measures in place, accidental extravasation does still occur, both from peripheral lines and from CVADs.

Prevalence

Risk factors

Prevalence

Extravasation is not as rare as some people may think. In cancer therapy experts estimate that it accounts for 0.5% to 6.0% of all adverse events associated with treatment.[4] But, when you consider that adverse events with cancer therapy are quite common, the absolute number of extravasations which take place is significant.[6]

Data regarding extravasation from CVADs is more limited. One small study estimated that extravasation occurs about 6% of the time.[4]

Risk factors

Some extravasations can be accounted for by error in the IV procedure, etc.[4,7] However, patients receiving these cancer therapies may have multiple risk factors that make IV infusion very difficult. For example, cancer patients – with a tendency for thin, fragile and mobile veins – are at higher risk of extravasation than the general population.[4]

In addition to factors relating to the procedure and to the patient, factors associated with the equipment/material used, concomitant medications and the treatments themselves can also increase the likelihood of extravasation. Some the most common factors known to increase the risk of extravasation are listed below:[4,8-10]

- Patient factors
  - ☐ Small blood vessels (e.g., infants and young children)
  - ☐ Fragile veins (e.g., elderly, cancer patients)
  - ☐ Hard, sclerosed veins
  - ☐ Mobile veins
  - ☐ Impaired circulation (e.g., cannula sited on side of mastectomy, lymphoedema)
  - ☐ Obstructed vena cava (elevated venous pressure can cause leakage)
  - ☐ Pre-existing conditions (diabetes, peripheral circulatory conditions like Raynaud's syndrome, radiation damage)
  - ☐ Obesity

- Trouble reporting symptoms early
  - ☐ Inability to report stinging/discomfort (e.g., sedated, confused)
  - ☐ Decreased sensation (e.g., as a result of neuropathy, diabetes, peripheral vascular disease)
- Cannulation and infusion procedure
  - ☐ Untrained or inexperienced staff
  - ☐ Multiple attempts at cannulation
  - ☐ Unfavourable cannulation site (e.g., back of hand vs. forearm, close to bone)
  - ☐ Bolus injection
  - ☐ High flow pressure
- Equipment
  - ☐ Steel butterfly needle
  - ☐ Catheter size and type
- Treatment
  - ☐ Ability to bind directly to DNA
  - ☐ Ability to kill replicating cells
  - ☐ Ability to cause tissue or vascular dilatation
  - ☐ pH
  - ☐ Osmolality
  - ☐ Characteristics of diluent

What are the implications of extravasation?

In general, extravasation is to be avoided. Even in patients who do not progress to ulcerative and necrotic tissue damage may still experience pain and discomfort, as well as indirect consequences, such as disruption of treatment and committing hospital resources to the management of extravasation.[3,4] The specific symptoms of extravasation, as well as their wider consequences, are discussed in this section.

Initial symptoms

The initial symptoms of extravasation occur immediately after the blood vessel has been breached. Depending on the agent and the patient extravasation may be accompanied by discomfort or pain, which can range from mild to intense. Patients often describe the pain as a burning sensation.[4]

The pain may be followed, in the next few hours, by erythema and oedema near the injection site.[3] In addition, there may be discolouration or redness of the skin near the site.[4]

The initial symptoms of extravasation are subtle, however, and can be similar for the extravasation of different agents (i.e., irritants vs. vesicants). The progression from these initial symptoms, however, differs greatly for irritants and vesicants – particularly relating to permanent damage to the tissue.[3]

Tissue damage

Vesicants, by definition, have the potential to cause tissue damage upon extravasation from the vein. Like the initial symptoms, the extent of tissue damage can vary greatly between different treatment regimens and patients.[4]

Tissue destruction caused by leakage of vesicants into surrounding tissue may be progressive in nature, and may happen quite slowly with little pain. Induration or ulcer formation is by no means an immediate phenomenon – as it takes time to develop.[5] In general, tissue damage begins with the appearance of inflammation and blisters at or near the site of injection. Depending on the drug and other factors, this can then progress to ulceration, and then in some

cases may progress to necrosis of the local tissue.[5] Necrosis can occasionally be so severe that function in the affected area cannot be recovered and surgery is required.[5]

If extravasation occurs in the forearm, the damage to tissue includes skin and subcutaneous tissue damage. If the extravasation occurs next to a nerve, ligament or tendon, then the damage can extend to that tissue and have an impact on sensation and function.[11]

Surgery

If vesicant extravasation is not recognised and dealt with promptly, the tissue damage can become so severe that surgical debridement and plastic surgery (possibly including skin grafting) may become necessary.[5] In the event that extravasation does affect nerves, ligaments or tendons, the damage may necessitate more extensive surgery.[4]

It is estimated that one third of vesicant extravasations give rise to ulceration. This ulceration, in combination with pain and necrosis, can be an indication for surgical intervention.[5,12]

Impact on cancer therapy

Most extravasation protocols call for the immediate cessation of the drug delivery, followed by measures to prevent further spread of the cancer drug into the tissue.[8,13–16] As a result, the delivery of cancer therapy may be delayed until the extravasation is resolved.

Some guidelines specifically address the issue of re-establishment of IV cancer therapy – recommending the establishment of an IV site in another limb.[13] However, most guidelines do not specifically address this process.[8,14–16]

Other consequences

Apart from the physical consequences, extravasation can lead to longer hospital stay, more consultations and increased length of follow-up care; the need for physical therapy; high treatment costs; psychological consequences (e.g., distress, anxiety); and even lost wages.[4] In addition, it is not uncommon for hospitals and their staff to be faced with a lawsuit following an extravasation.[5]

All of these factors contribute to the seriousness of an extravasation, and can add to the toll on the patient, their family and the healthcare system. One of the primary goals of extravasation protocols and guidelines is to educate healthcare professionals about the avoidance of serious complications and preventions of extravasations before patients require surgical processes.

How is extravasation recognised?

It is critical that an extravasation is recognised and diagnosed early. The most effective way to recognise and detect extravasation in its early stages is to be aware of and act on all relevant signs and symptoms. Telltale signs and symptoms can be gathered from patient reports, simple visual assessment of the injection site, and careful monitoring of the IV device. Then, once an extravasation is suspected, it will also be important to rule out other possible conditions, such as flare reaction.[4,7]

The quality of the nursing assessment during administration can play a key role in minimising frequency and severity, since delays in the recognition and treatment of vesicant extravasation increase the likelihood of developing tissue damage and necrosis.[4,17]

Since extravasation could have serious consequences, a second opinion is always warranted. If there is any doubt as to whether or not it has occurred, stop and ask for help.

Patient reporting

Patients need to know the possible side effects of the treatments they are receiving. In the case of extravasation, it is recommended that the patient be told about the possible complications and to be aware of any pain/sensation at the site of infusion. Patients should feel that they can report any strange sensations as soon as they arise, so the healthcare team can take these symptoms into account.

The most important patient-reported symptoms for assessing extravasation relate to the sensation around the site of injection – or, in the case of a central line, around the CVAD and surrounding area. Typically these complaints include:[8,18]

- Pain
- Swelling
- Redness
- Discomfort
- Burning
- Stinging
- Other acute changes at the site of extravasation

None of these are confirmation of an extravasation on their own, but should be treated with concern and warrant further examination, such as testing the patency of the infusion with blood return. In addition, the nature of the complaints should be verified against the signs and symptoms of other possible diagnoses.

Visual assessment

Visual signs, while by no means exclusive to extravasation, do provide useful confirmation for patient reports in suspected extravasation. The common signs, occurring at or around the site of the cannula – or, in the case of central line around the CVAD and the surrounding area – include:[8,18,19]

- 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.[7]

Checking the infusion line

Apart from patient reporting and visible symptoms of extravasation, it is possible to determine whether extravasation has occurred by checking the infusion line itself. Verification of the line should be used to help confirm any suspected extravasation (peripheral or central line), if possible.

Signs of extravasation, in relation to the cannula, include:[8,18]

- Increased resistance when administering IV drugs
- Slow or sluggish infusion
- Change in infusion flow
- Lack or loss of blood return from the cannula

Look for blood return (flashback) upon insertion of the needle. If the needle is in the lumen of the vein, you should notice some blood return. If you confirm blood return, the cannula can be glided carefully into position, ready to stop if met with any resistance.

Brief blood return may be seen if the needle passes through the lumen of the vein and then out the other wall. However, the return will halt once the needle has passed the posterior venous wall.[20] If this occurs, the needle has passed through the lumen and anything infused will be administered straight into the surrounding tissue. The cannula should be removed and the procedure recommenced using another vein, if necessary in another vein above the original site on the same vein (closer to the heart).[7]

Distinguishing extravasation vs. other conditions

Distinguishing between extravasation and other local reactions is an important step in diagnosis. Initially, making the distinction can be very difficult and requires sound clinical judgment. Familiarity with the different symptoms increases the likelihood of appropriate treatment. In the case of extravasation, that means that interventions and management will be initiated at an early stage and help to prevent some of the more serious consequences associated with it.[4,8]

Other conditions that resemble extravasation include:[4,7,8,18]

- Flare reaction
- Vessel irritation
- Venous shock
- Phlebitis
- Hypersensitivity

The principal differences between extravasation and these conditions relate to the nature and timing of the patient's complaints, the type and extent of erythema noted and the location and presence of swelling.[4,8] A guide describing symptoms and differences between conditions commonly associated with IV infusion can be found in Appendix 2.

How is extravasation prevented?

The most important approach to minimising the consequences of extravasation is prevention.[12] Healthcare professionals involved in the handling and administration of IV cancer therapies should become familiar with their local procedures and protocols and develop an understanding of the important precautionary steps that should be taken to avoid extravasation and the resulting injuries.

Given this cautious and systematic approach, most episodes of extravasation can be avoided altogether.[21] The following sections provide advice for good practice and may help prevent extravasation and minimise injury.

Standard procedures

Local policies and protocols for preventing, identifying risk factors, diagnosis, and managing extravasation represent one of the best ways with which to combat extravasation in the clinical setting. The protocols should be drug specific and be developed with input from the whole healthcare team involved.

If they are already in place, efforts should be taken to make them readily available to all who require them (i.e., those healthcare professionals involved in the administration of IV cancer therapy).[22] If protocols do not exist, efforts should be made to formally document the local procedures for dealing with extravasations.

There are several examples of existing policies and protocols; some of them can even be found online (see references section).[2,13–16]

Training

As mentioned above, local policies and protocols are very important for the delivery of quality cancer care. As well as making these documents available, active education of the relevant staff members including doctors, would help to keep the standard of care at a consistently high level across the board.[18] All staff should be encouraged to regularly review the relevant literature on cytotoxics handling and relating to new agents, as part of their ongoing training.[22]

Those involved in the administration of IV cancer therapies should be educated on the techniques of IV infusion as well as the local organisational policies for:[18]

- Venous access
- Venous assessment
- Administration of chemotherapy
- Management of extravasation
- Management of hypersensitivity, etc.

Patient education

With regard to extravasation, communication with the patient is very important, since they are being relied upon to report symptoms critical in its recognition.

Using positive language, patients should be told about the nature of the cancer therapy they are receiving and the real possibility of side effects. They should be asked to report any change in sensation, stinging or burning, no matter how insignificant it appears to them. An informed patient can then help to recognise extravasation early and should always be listened to.[11]

In addition, training relating to meeting the information needs of patients within cancer care, for example presenting a positive approach to delivering information vs. a negative one: "XXX is a possible side effect, but we can't predict your reaction; most patients take these drugs and tolerate them well."[11]

Equipment selection

The choice of equipment/material for administering cancer therapy is important when trying to minimise the risk of extravasation. Important considerations include the size and type of cannula or catheter, and whether to use a subcutaneous device or a central line.

In general, the goal is to choose a needle that is least likely to become dislodged, and one that allows the blood to flow around it. As a rule, it is advisable to use the smallest gauge cannula in the largest vein possible. Specific recommendations include:[4,7,12,20]

- Use of a small bore plastic cannula (1.2–1.5 cm long)
- For peripheral access, short, flexible polyethylene or Teflon
- Use a clear dressing to secure the cannula – to allow for constant inspection
- Secure the infusion line, but never cover the line with a bandage (the insertion point must always be visible)

Vein selection in peripheral administration

The choice of vein for the infusion is an equally important consideration for the prevention of extravasation. Finding the largest, softest and most pliable vein is the best choice to avoid complications.[9] Some general guidelines include:[8,12,18]

- Try to use the forearm, not the back of the hand
- Avoid small and fragile veins
- Avoid insertion on limbs with lymphoedema or with neurological weakness
- Avoid veins next to joints, tendons, nerves or arteries
- Avoid the antecubital fossa (area near the elbow)

For a more detailed overview of vein selection please refer to Appendix 3.

If a first attempt to insert a cannula failed, the second insertion should be made above (closer to the heart) the original site if possible. In general, it is thought that it is best to avoid administering cytotoxic drugs below a previous venepuncture site.[7]

Administering intravenous treatment

In addition to careful selection of equipment and veins for administration of IV cancer therapy, there are many precautions that can be considered during the infusion to help reduce the risk of extravasation.[8,12,18,22]

Starting IV treatment: [8,12,18,22]

- Become familiar with the manufacturers' recommendations for administration of each treatment
- Dilute drugs to the recommended concentrations and give at the appropriate rate
- Check blood return from the cannula, or CVAD, prior to administration
- Before administering therapy, flush the line with saline (sodium chloride 0.9%) or glucose 5% (as well as between infusions)
- Ensure that the cannula is secure during the administration of drugs – the appropriate dressing (e.g., IV OPSITE 3000, VecaFix or Tegaderm IV) should be used
- Never cover the insertion point (i.e., cover cannula site with a bandage)
- If in doubt re-cannulate

Monitoring IV treatment:[8,12,18]

- Check for swelling, inflammation, redness and pain around cannula site during administration of IV drugs
- Check blood return from the cannula when vesicants are administered
- Question the patient about any possible symptoms (i.e., heat, pain and swelling during administration)
- Do not allow patients receiving intravenous infusions of vesicant drugs to leave clinical area

Considerations for vesicants:[8,12]

- Whenever possible always give vesicant drugs into a recently inserted cannula
- Patients receiving repeated doses of potentially harmful drugs peripherally should have the cannula resited at regular intervals – every few days (depending on hospital recommendations)
- Consider the order of the infusions being given – attempt to administer treatments so vesicants present the least risk to the patient
- A CVAD could be considered if veins are very difficult to access. This might minimise the risk of extravasation
- In no case should a butterfly needle be used for any chemotherapeutic infusion

How is extravasation managed?

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 caused by the extravasated drug.[22] In general the management of extravasation includes detection (covered in the "How is extravasation recognised?" section), analysis and action.[23]

Procedures and protocols

Just as they play a key role in the prevention of extravasation, local procedures and protocols are paramount in the timely recognition and management of extravasation and the prevention of serious tissue damage.

If they are already existing, efforts should be made to make them readily available to all who need them (i.e., those healthcare professionals involved in the administration of IV cancer therapy).[22] If protocols do not exist, efforts must be made to formally document the local procedures for dealing with extravasations.

It is highly recommended that all healthcare professionals involved in the administration of IV cancer therapy should be aware of:[22]

- The extravasation policy
- The contents and whereabouts of the extravasation kit and a replacement kit

There are several examples of existing policies and protocols which can be found online.[2,13–16]

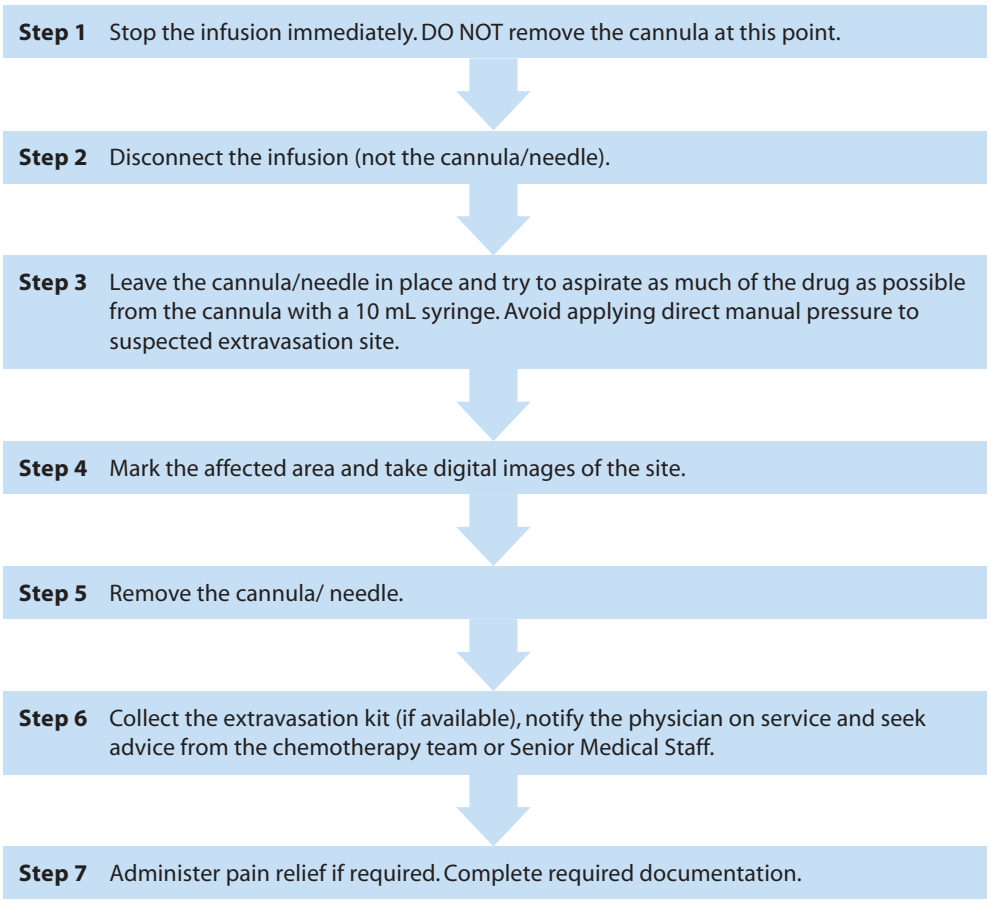
Specific courses of action depend on the nature of the drug, how much of it has extravasated and where.[3] Delays in recognition and treatment can increase the risk of tissue necrosis.

If extravasation is suspected, treatment should begin as soon as possible as commencing treatment within 24 hours can reduce damage to tissues, however, extravasation may only become apparent 1–4 weeks after the administration.[3]

No matter what the nature of the drug, if extravasation is suspected the initial response remains the same. The most important thing initially is to limit the amount of drug extravasating into the surrounding tissue.[13–16,22] Depending on your hospital or centre, there may be prescribed steps and procedures to undertake before any action is taken (i.e., getting a physician's signature on the extravasation protocol)

In general, the first course of action is to stop the infusion, aspirate as much of the infusate as possible, mark the site and then remove the cannula (while continuing to aspirate from the extravasation site). Elevate the affected limb and administer analgesia if required.[8,15] If possible take a digital image of the extravasated area. Then, depending on the drug being infused, the correct protocol should be followed to determine the next steps. An example protocol is illustrated in Figure 1.

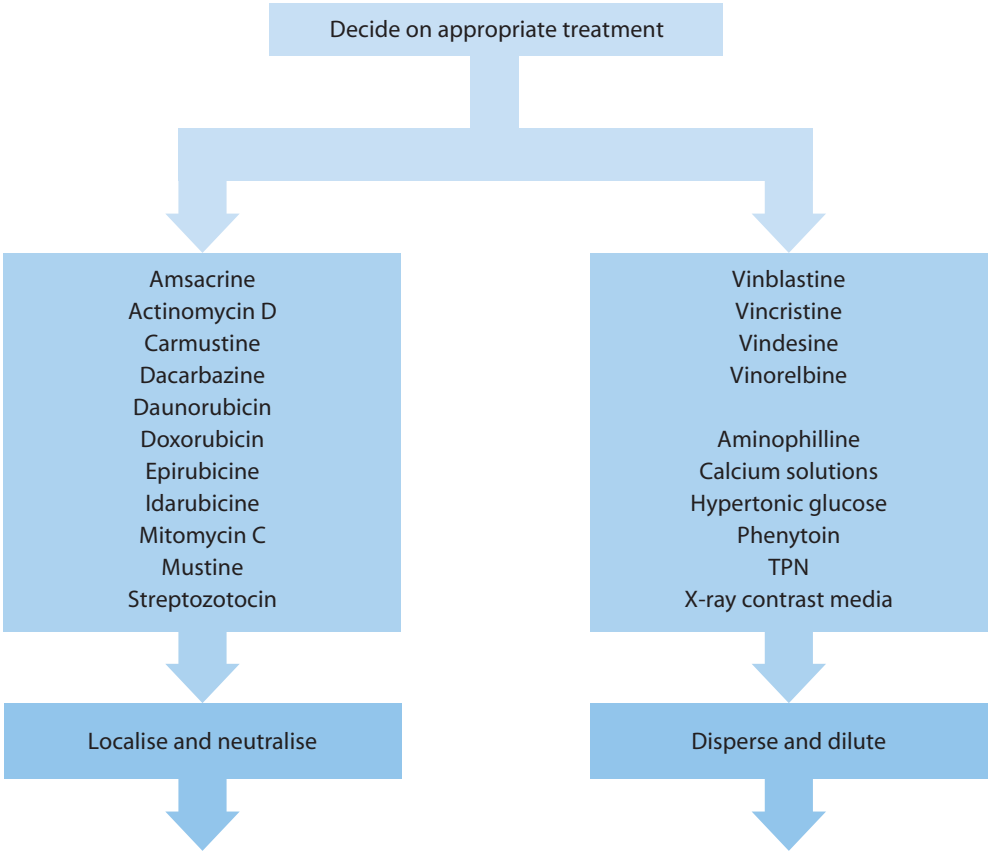
Figure 1. Management of extravasation.[8]



NOTE: STEP 8 onwards appear in Figures 3, 4 and 5, depending on whether the extravasation requires *Localisation and neutralisation* or *Dispersion and dilution*. How to determine which pathway to follow is described in the following sections.

From this point forward, the nature of the treatment prescribed by the presiding physician or hospital policy will depend on the drug, which has extravasated. Figure 2 shows the decision pathway as it relates to individual treatments.

Figure 2. Decide on appropriate treatment.[8]



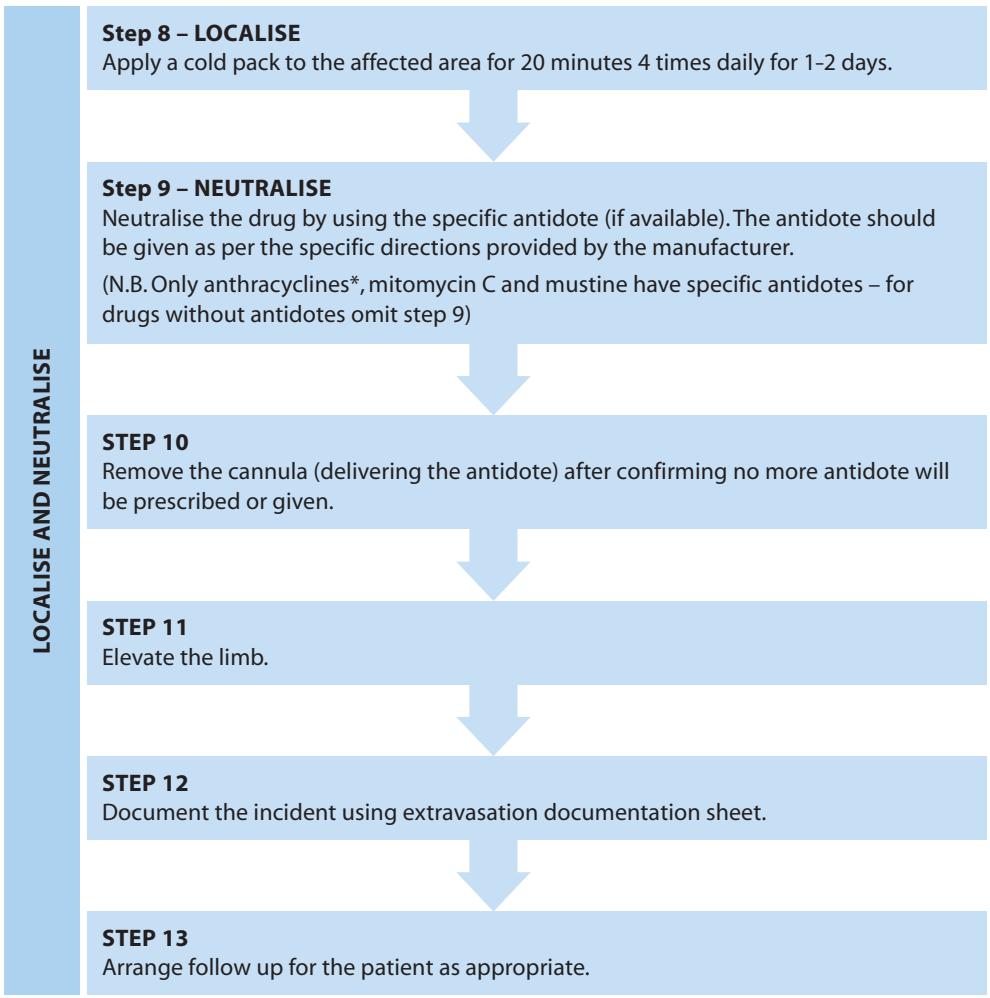
If the drug is a non-vesicant, application of a simple cold compress and elevation of the limb may be sufficient to limit the swelling etc.[8] In contrast, the extravasation of a vesicant requires several steps and differs for the various classes of drug. There are two broad approaches to limiting the damage caused by extravasation: localisation and neutralisation; or dispersion and dilution.[8]

Localise and neutralise strategy (Figure 3):[8]

- Use cold compresses to limit the spread of infusate. It used to be thought that cold limited spread through vasoconstriction. In animal models, it appears that cold prevents spread by a mechanism other than vasoconstriction – suggested to be decreased cellular uptake of drug at lower temperatures
- Consider using antidotes to counteract vesicant actions.

Figure 3. Localise and neutralise.[8]

NOTE: The initial steps leading to STEP 7 are described in Figure 1.



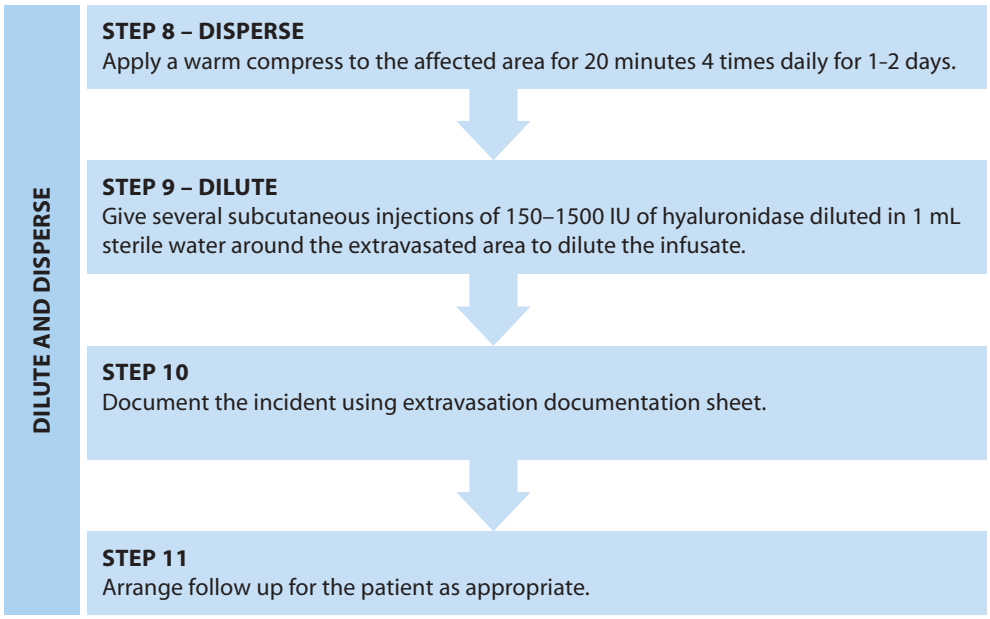
*For a detailed list of anthracyclines, please refer to Appendix 1)

Disperse and dilute strategy (Figure 4):[8]

- Appropriate for the extravasation of vinca alkaloids
- Use warm compresses to prompt vasodilation and encourage blood flow in the tissues, thereby spreading the infusate around
- Consider using hyaluronidase to dilute infusate

Figure 4. Disperse and dilute.[8]

NOTE: The initial steps leading to STEP 7 are described in Figure 1.



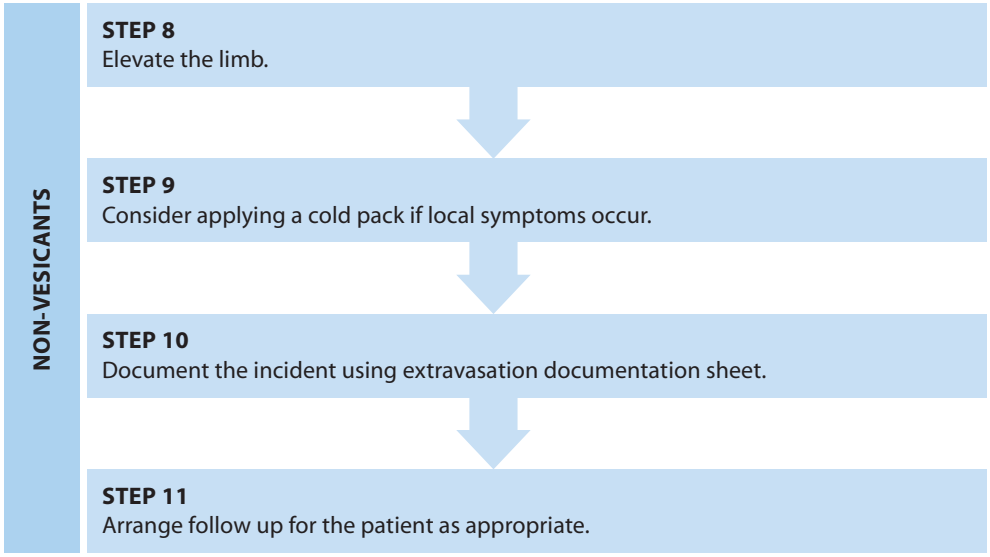
In addition, measures can be taken to limit inflammation, discomfort and pain.[22]

- A saline flush out technique could also be used – but this approach requires specialist advice
- Corticosteroids can be given to treat inflammation – although there is little evidence to support their use in extravasation
- Antihistamines and analgesics may be required for relief of pain and other symptoms

If the infusate is a non-vesicant, the procedure is similar to localise and neutralise, but does not involve any antidotes.[8] A step-by-step approach for non-vesicants is shown in Figure 5.

It is worth noting that beyond the measures described here, unfortunately, the management of extravasation is not well standardised due to a lack of documented evidence. As such, extravasation and often calls for specialist advice.

Figure 5. Treatment for non-vesicants.[8]



Antidotes

Antidotes are agents applied or injected to the extravasated area to counteract the effects of the infiltrated agent – usually vesicants. They form an important part of the "localise and neutralise" and the "disperse and dilute" strategies. For example, Savene™ (dexrazoxane) can help to neutralise anthracyclines; whereas hyaluronidase helps to facilitate the dilution of vinca alkaloids into the surrounding tissues. Provided they are used in the appropriate way and for the appropriate infusate they might help to prevent progression to ulceration, blistering and necrosis. The evidence supporting the use of different antidotes is often inconclusive and their use (including pros and cons) should be carefully considered.

Antidotes currently available used for treating extravasation (and their proposed mechanism) include:[12,24–28]

- Savene™ (dexrazoxane): The only registered antidote for anthracyclines, inhibits DNA topoisomerase II, which is the target of anthracycline chemotherapy, blocking the enzyme so it is no longer affected by anthracyclines and damage to the cells is averted
- Dimethylsulfoxide (DMSO): Prevents ulceration. May work by virtue of its free radical scavenging property
- Sodium thiosulfate: Prevents alkylation and subsequent destruction in subcutaneous tissue by providing a substrate for alkylation
- Hyaluronidase: Breaks 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

Table 1. Antidote use after extravasation.[12*]

Extravasated drug	Suggested antidote	Level of evidence	Advice
Anthracyclines	Savene™ (dexrazoxane)	Efficacy in biopsy-verified anthracycline extravasation has been confirmed in clinical trials.	3 day course of Savene™ treatment: 1000 mg/m^2 IV as soon as possible (no later than 6 hours) after extravasation on day 1; 1000 mg/m^2 on day 2; and 500 mg/m^2 on day 3 See Appendix 4 for full details
Anthracyclines	Topical DMSO (99%)	Suggested as a possible antidote in many literature sources. Due to lack of evidence it is recommended that this is further studied	Apply locally as soon as possible. Repeat every 8 hours for 7 days See Appendix 5 for full details
Mitomycin C	Topical DMSO (99%)	Suggested as a possible antidote in many literature sources. Due to lack of evidence it is recommended that this is further studied	Apply locally as soon as possible. Repeat every 8 hours for 7 days See Appendix 5 for full details
Mechlorethamine (Nitrogen mustard)	Sodium thiosulfate	Due to lack of evidence, this antidote is not recommended	2 mL of a solution made from 4 mL sodium thiosulfate + 6 mL sterile water for subcutaneous injection
Vinca alkaloids	Hyaluronidase	Suggested as a possible antidote in many literature sources. Due to lack of evidence it is recommended that this is further studied	150–1500 IU subcutaneously around the area of extravasation See Appendix 6 for full details
Taxanes	Hyaluronidase	Suggested as a possible antidote in many literature sources. Due to lack of evidence it is recommended that this is further studied	150–1500 IU subcutaneously around the area of extravasation See Appendix 6 for full details

*For a detailed list of vesicants, please refer to Appendix 1)

Anthracycline extravasation

For anthracycline extravasation, a new treatment, Savene™, and the data supporting it is changing the way antidotes are recommended in the "localise and neutralise" strategy.

In the past, several protocols and policies suggested the use of topical DMSO (99%) to stop the development of ulcers in anthracycline extravasation.[12] In the past few years, new data from preclinical and clinical studies has changed the way antidotes are used in anthracycline extravasation, particularly that for Savene™.[29–32] And, it has since become the only licensed specific antidote to anthracycline extravasation.

As a result, more recent guidance in this area recommends the use of Savene™ in the treatment of anthracycline extravasation from both a central- and a peripheral line.[2]

Extravasation kit

The idea behind the extravasation kit is to store all the drugs and equipment that would be used in an emergency situation. The kit should be put together to deal with any eventuality, including extravasation of a variety of vesicant drugs.[19] The kit should be checked regularly and restocked from pharmacy following use.[22]

An example of a recommended extravasation kit can be found in Appendix 7.

Surgery and debridement

Even if extravasation is identified early, progressive extravasation can give rise to ulcerated and necrotic tissue over time. However, the early steps to prevent and manage extravasation help to limit the need for surgery.[5]

Ulcerative cases caused by anthracycline extravasations are common (about ⅓ of all cases), therefore surgery should not be considered as the initial primary treatment of choice.[4] When there is ulceration or continued pain, surgical intervention is indicated to excise the damaged tissue.

In general, the goal of surgery is to remove the damaged tissue and the vesicant infusate to prevent progression of the extravasation, as well as to restore function and reduce pain to the affected area.[5] Once this tissue is removed, the remaining wound often needs to be closed. The options for wound closure include skin flap and skin grafts (from other areas of the body).[5] In most cases, the surgeon would opt for a wait and see conservative approach – to establish whether ulceration will occur naturally and to attempt to avoid surgery and skin grafting.[12] However, in cases where there is pain, surgical debridement of the extravasated area must be considered 24 hours to 1 week after an extravasation.[12]

Documentation and reporting

Each incident of extravasation must be thoroughly documented and reported.[23] 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

In different centres, the documentation procedure may differ slightly between organisations, however the information collected will be very similar. Following an extravasation, the following details should be documented:[15,18,23]

- 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

In addition to the initial documentation, the extravasated area should be checked and any changes documented every 8 hours. Any oedema, erythema, stinging, burning, pain, or fluid leakage at insertion site should be included in this report.[15]

A couple of examples of extravasation documentation forms have been included for your reference in Appendix 8.

Summary

Managing extravasation in accordance with the latest scientific understanding and medical consensus allows for optimal treatment to be delivered across different regions. By following the example set out in this module, which includes the latest information on extravasation and a selection of current protocols and policies from prominent centres,[8,13–16] nurses and other healthcare can help to raise the standard of care in cancer therapy.

Nurses have a key role to play in implementing these improvements to practice. As outlined in this module, they have a unique interaction with the patient and play a large part in the administration of IV cancer therapy. By learning how to effectively recognise extravasation and by becoming familiar with all the local protocols for dealing with it, including the use of antidotes nurses can help to minimise the incidence of this complication of cancer treatment.

Nurses also have the opportunity to play a lead role in expanding the use of best practice in this area. They can help to initiate and develop local protocols and policies where there aren't any due to their role in administration of the drugs and thanks to their knowledge of the patient and unique perspective regarding extravasation management.

By helping to broaden the understanding of extravasation and its management across the nursing and other healthcare professions, it is hoped that this educational module will achieve its objective of improving prevention and overall management of extravasations in cancer patients by utilising the latest available evidence.

Appendix 1. List of drugs: vesicants, irritants and non-vesicants.[8,12,15]

Vesicants

DNA-binding

Alkylating agents

Mechlorethamine
(Nitrogen mustard)

Anthracyclines

Daunorubicin
Doxorubicin
Epirubicin
Idarubicin

Others

Dactinomycin
Mitomycin C

Non-DNA-binding

Vinca alkaloids

Vinblastine
Vincristine
Vindesine
Vinorelbine

Irritants

Carmustine
Cyclophosphamide
Dacarbazine
Etoposide
Fluorouracil
Ifosfamide
Mephalan
Mitoxantron
Streptozocin

Possible irritants[2]

Carboplatin
Cisplatin
Docetaxel
Irinotecan
Oxaliplatin
Paclitaxel
Topotecan

Non-vesicants[1]

Asparaginase
Bleomycin
Bortezumib
Cladribine
Cytarabine
Etoposide phosphate
Gemcitabine
Interferons
Interleukin-2
Methotrexate
Monoclonal antibodies
Pemetrexed
Raltitrexed
Thiothepa

[1] Any agent extravasated in high enough concentration may be an irritant.

[2] There have been few reports of these agents acting as irritants, but there is no clear evidence for this.

NOTE: For those medications that are not considered a vesicant but cause prolonged patient discomfort at the infusion site, it is strongly recommended that a central line be placed.

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Appendix 2. Distinguishing extravasation from other conditions[4,7,8]

Characteristic	Flare reaction	Vessel irritation	Venous shock*	Extravasation
Presenting symptoms	Itchy blotches or hives; pain and burning uncommon	Aching and tightness	Muscular wall of the 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 appears suddenly and dissipates within 30–90 minutes	Usually appears within minutes after injection. Colouration may 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

* Can be caused by very cold drugs or by rapid administration.

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Appendix 3. Vein selection procedure.[11]

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/antecubital fossa	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 line
Least desirable	UNSATISFACTORY VEIN / UNDESIRABLE LOCATION veins in forearm/hand not palpable or visible	Consider central venous line

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Appendix 4. Administering Savene™ (dexrazoxane).[2,26]

Savene™ is the only licensed treatment for anthracycline extravasation (doxorubicin, epirubicin, daunorubicin, idarubicin).

Steps for administration:

1) Follow steps for localisation and neutralisation of extravasation (Figure 1 and Figure 3)
2) Administration of Savene™ should begin as soon as possible and no later than 6 hours after the accident
3) Remove ice packs (or other cooling procedures) from the area at least 15 minutes before the administration of Savene™
4) Reconstitute Savene™ with 25 mL sterile water before further dilution in diluent
5) Give Savene™ as an intravenous infusion once daily for 3 consecutive days according to body surface area:
   a. Day 1: 1000 mg/m^2
   b. Day 2: 1000 mg/m^2
   c. Day 3: 500 mg/m^2
6) For patients with a body surface area of more than 2.0 m^2 the single dose should not exceed 2000 mg on day 1 and day 2 and 1000 mg on day 3

Please refer to Savene™ prescribing information for a full list of contraindications, precautions and warnings.

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Appendix 5. Administering dimethylsulfoxide.[25]

Dimethylsulfoxide (DMSO 99%) is an option for the treatment of extravasation with anthracyclines, mitomycin C, doxorubicin, idarubicin, epirubicin and actinomycin D. DMSO/corticosteorids should not be used.

Steps for administration:

1) Follow steps for localisation and neutralisation of extravasation (Figure 1 and Figure 3)
2) Draw around area with indelible pen
3) Put gloves on
4) Apply thin layer of DMSO topically to the marked area
5) Allow it to dry
6) Apply a non-occlusive dressing
7) This should be applied within 10–25 minutes
8) Check for erythema caused by DMSO

Please refer to DMSO 99% prescribing information for a full list of contraindications, precautions and warnings.

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Appendix 6. Administering hyaluronidase.*[27]

Hyaluronidase may be indicated for suspected or known extravasation of: dextrose in concentration of >10%; parenteral alimentation solution (glucose or protein); solutions containing calcium or potassium; aminophylline; antibiotics. In addition, there are recommendations for hyaluronidase in response to vinca alkaloid extravasation.[12]

Steps for administration:

1) Follow steps for dispersion and dilution of extravasation (Figure 1 and Figure 4)
2) Administration of hyaluronidase should begin within 1 hour of extravasation for best results
3) Dilute 150–1500 IU of hyaluronidase in 1 mL sterile water
4) If there is no blood return in the affected IV catheter, consider infusing 0.4 CC of dose directly through the affected IV catheter before removing the catheter and administering the remainder of the dose subcutaneously around the periphery extravasation
5) Use 25 or 27 gauge needle and change after each injection
6) Subcutaneously (or intradermally) inject 1 ml (150 IU) of hyaluronidase as 5 separate 0.2 mL injections around the periphery of extravasation site

* Hyaluronidase is not available in all countries

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

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Appendix 7. Extravasation kit.[19]

Below is an example of a typical extravasation kit, which included:

- Instant cold pack
- Instant hot pack

(Or a reusable pack, which can be use for both)

- Antidotes according to local procedures
- 2 mL syringes
- 25 G needles
- Skin disinfectant as per local guidelines (e.g., alcohol swabs)
- Indelible pen for marking the affected area
- Documentation forms
- Copy of extravasation management procedure
- Patient information leaflet

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Appendix 8. Documentation template

General extravasation template.[33]

Patient's initials |_____|_____| (First name second name) Date of birth: |___|___|___| (Day month year)

Extravasation of cytotoxic agents – Documentation (I)

Cannula used: ○ Butterfly® ○ Venflon® ○ Other. . . . . .
Diameter . . . . . G
Cannula fixated with: . . . . . .

Site of puncture:
○ Left arm ○ Right arm ○ Port-a-cath system
○ Forearm ○ Antecubital fossa ○ Central venous catheter
○ Wrist ○ Dorsum of hand
○ Other . . . . . .

Was it necessary to puncture the same limb more than once?
○ Yes ○ No

Where – in relation to the original puncture site – was the vein punctured?
○ Proximal ○ Distal ○ Medial/lateral

Has the patient any of the following symptoms:
→ Upper blockage to inflow: ○ Yes ○ No
→ Lymphoedema (same arm): ○ Yes ○ No
→ Haematoma (same arm): ○ Yes ○ No

Sequence of application:

Amount	Substance or trade name	Volume	Extravascular	
1.	mg	in	ml	○ extravascular
2.	mg	in	ml	○ extravascular
3.	mg	in	ml	○ extravascular
4.	mg	in	ml	○ extravascular
5.	mg	in	ml	○ extravascular

Estimated volume of extravasated drug: . . . . . ml
Type of administration: ○ i.v. ○ i.a.
○ Bolus ○ Infusion ○ Infusion pump

Patient's initials |____|____|
First name second name

Date of birth: |___|___|___|
Day month year

Extravasation of cytotoxic agents – Documentation (II)

Extravasation recognised: Date |___|___|___| Time of day: .....
Day month year

- ○ During administration
- ○ Immediately after administration
- ○ ..... hours after administration
- ○ ..... days after administration

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

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

Information for/ instructions to patient: |___|___|___|
Day month year

(Plastic) surgeon consulted: ○ Yes |___|___|___| ○ No
Day month year

Next control appointment: |___|___|___| Time: .....
Day month year Ward: .....

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

E-mail: .....

Affiliation: .....

Patient's initials |_____|_____|
First name second name

Date of birth: |___|___|___|
Day month year

Extravasation of cytotoxic agents – Documentation (III)

	✓ = Applies	↑ Deterioration		= No change		↓ Improvement	
	Status post paravasationem	1. Control	2. Control	3. Control	4. Control	5. Control	6. Control
Date							
Paraphe of doctor							
Symptoms after extravasation:							
Pain (burning, stinging)							
Oedema							
Erythema							
Blistering							
Discolouration							
Induration							
Functional impairment							
Ulceration							
Necrosis							
Demarcation							
Formation of eschar							
Infection							
Complete healing							
Extent of extravasation:							
Two biggest diameters in cm							
Measures:							
Conservative measures							
Surgical measures: Excision							
Transplantation							

Notes:

Specific extravasation template*

Extravasation of anthracycline **Observation and prescription form**

Name: **Height/weight _____/_____**

Date of birth: **Surface (m2) _____**

Telephone number:

Time/Day	0-6 hrs	Day: __	Day: __	Day: __	Day: __	Day: __	Day: __	Day: __	Day: __
Observation Date:									
Observation Time:									
Time of extravasation									
Location of Extravasation									
Describe IV access from which Extravasation occurred									
Aspiration on catheter (yes/no)									
Size of the affected area (cm x cm)	x	x	x	x	x	x	x	x	x
Name of anthracycline diluent									
Amount of fluid extravasated	ML								
Amount of anthracycline extravasated	Mg								
Local ice treatment (yes/no) Remove at least 15 min before Savene ™									
Other local treatment (yes/no) If yes describe									
Describe symptoms listed below using yes/no or use CTC grades none, mild, moderate, severe									
Date									
Local swelling									
Local redness									
Local blistering									
Local necrosis									
Pain									
Sensory disturbances									
Skin atrophy									
Impaired limb function									
Disfigurement									
Other:									
Other:									

	Day 1	Day 2	Day 3	Savene™ dosage to be administered: Day 1 and 2: 1000 mg/ m2, Day 3: 500 mg/m2 Max surface 2.0 m2
Date				
Savene ™ infusion (mg/total)				
Start time of Savene ™ infusion				
Stop time of Savene ™ infusion				
Signature doctor				
Signature nurse				

*Treatment of anthracycline extravasation in mice with dexrazoxane with or without DMSO and hydrocortisone, LANGER Seppo W, Cancer chemotherapy and pharmacology 2006, vol. 57, no1, pp. 125-128.

Additional comments:

* By courtesy of TopoTarget A/S

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References

1. Jones L, Coe P. Extravasation. *Eur J Oncol Nurs* 2004;**8**:355–358.
2. Jackson G, Buter J, Cavenagh J, *et al.* Consensus opinion on the use of dexrazoxane (Savene™) in the treatment of anthracyclines extravasation. Consensus Meeting Report 2006.
3. Ener RA, Meglathery SB, Styler M. Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004;**15**:858–862.
4. McCaffrey Boyle D, Engelking C. Vesicant extravasation: myths and realities. *Oncol Nurs Forum* 1995;**22**(1):57–67.
5. Rudolph R, Larson DL. Etiology and treatment of chemotheraupeutic agent extravasation injuries: a review. *J Clin Oncol* 1987;5(7):1116–1126.
6. Weiner MG, Ross SJ, Mathew JI, *et al.* Estimating the costs of chemotherapy-associated adverse event clusters. *Health Serv Outcomes Res Method* 2007: In print.
7. Wood LS, Gullo SM. IV vesicants: how to avoid extravasation. *Am J Nurs* 1993;**93**(4):42–46.
8. Whiteland M. Policy for the management of extravasation of intravenous drugs. 2001. Available at: www.cancerresource.co.uk/nursing%20developments/extravasation%20policy.pdf
9. Pan-Birmingham NHS. Guidelines for the Management of Extravasation. Available at: www.birminghamcancer.nhs.uk/viewdoc.ashx?id=oHV9ZQbj92im6AaanFEnvw%3D%3D
10. National Extravasation Information Service website. Available at: http://www.extravasation.org.uk/home.html.
11. Hughes CB. Giving cancer drugs IV: some guidelines. *Am J Nurs* 1986;**86**(1):34–38.
12. Schrijvers DL. Extravasation: a dreaded complication of chemotherapy. *Ann Oncol* 2003;**14**(Suppl 3):iii26-iii30.
13. Pharmaceutical Sciences, Vancouver General Hospital. Appendix II: Extravasation of antineoplastic agents. 2007 Revision. Available at: www.vhpharmsci.com/PDTM/APDX7i.htm.
14. Children's Hospital Medical Center. II-113 Vesicant Chemotherapy Extravasation. 2003 Revision. Available at: www.cincinnatichildrens.org/NR/rdonlyres/390692D4-CD68-4CD8-A4FA-82F1CF3DD259/0/II113.pdf.
15. Medical University of South Carolina (MUSC). Work practice policy for personnel dealing with cytotoxic (antineoplastic) drugs. 2005 Revision. Available at: www.musc.edu/fanda/risk/oshp/safetymanual03/cytodrug.pdf.
16. Co-operative Cancer Departments, Denmark. Paravenous cytostatica administration. December, 2006.
17. Loth TS, Eversmann WW Jr. Treatment methods for extravasations of chemotherapeutic agents: a comparative study. *J Hand Surg* 1986;**11**(3):388–396.
18. Polovich M, White J, Kelleher L. Chemotherapy and biotherapy guidelines and recommendations for practice, 2nd ed. Oncology Nursing Society, 2006.
19. Allwood M, Stanley A, Wright P, eds. *The cytotoxics handbook.* 3rd ed. Oxford: Radcliffe Medical Press Ltd., 1997.
20. Hadaway LC, Millam DA. On the road to successful IV starts. *Nursing* 2005;**35**:1–14.
21. Bertelli G. Prevention and management of extravasation of cytotoxic drugs. *Drug Safety* 1995;**12**(4):245–255.

22. Management and Awareness of the Risks of Cytotoxics Group. Managing cytotoxic extravasation. 2007.

23. Dougherty L and Lister S. Chapter 10: Drug administration: cytotoxic drugs. The Royal Marsden Hospital Manual of Clinical Nursing Procedures, 6th ed. Blackwell Science, 2004, 233–245.

24. de Lemos ML. Role of dimethylsulfoxide for management of chemotherapy extravasation. *J Oncol Pharm Pract* 2004;**10**(4):197–200.

25. Bertelli G, Gozza A, Forno GB, *et al.* Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective study. *J Clin Oncol* 1995;**13**(11):2851–2855.

26. Savene™ Summary of Product Characteristics. TopoTarget A/S, Copenhagen, Denmark, 2006.

27. Treatment of extravasation of IV fluids: hyaluronidase. 2006. Available at: http://info.med.yale.edu/pediat/pedres/Policies/NICU%20Guidelines%202006/YNHH%20NBSCU%20PDF%20Guidelines%20wo%20stats%20Aug06/Treatment%20of%20Extravasation%20of%20IV%20fluids-Hyaluronidase%20Jul06.pdf.

28. Shamseddine AI, Khalil AM, Kibbi AG, *et al.* Granulocyte macrophage-colony stimulating factor for treatment of chemotherapy extravasation. *Eur J Gynaecol Oncol* 1998;**19**:479–481

29. Sauerland C, Engelking C, Wickham R, Corbi D. Vesicant extravasation part I: Mechanisms, pathogenesis, and nursing care to reduce risk. *Oncol Nurs Forum* 2006;**33**(6):1134–1141.

30. Wickham R, Engelking C, Sauerland C, Corbi D. Vesicant extravasation part II: Evidence-based management and continuing controversies. *Oncol Nurs Forum* 2006;**33**(6):1143–1150.

31. Mouridsen HT, Langer SW, Buter J, et al. Treatment of anthracycline extravasation with Savene (dexrazoxane). Results from two prospective clinical multicenter studies. *Ann Oncol* 2007;**18**(3):546–550

32. Schulmeister L. Totect™: A new agent for treating anthracycline extravasation. *Clin J Oncol Nurs* 2007:**11**(3):387-395.

33. Mader I, Furst-Weger PR, Mader RM, *et al. Extravasation of Cytotoxic Agents.* Vienna: Springer-Verlag, 2003.