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Complications of intravenous nutrition

Introduction

Intravenous nutrition (IVN) can cause a range of complications, including traumatic, infective, thrombotic and metabolic problems. At best, these require skill and resources to overcome whereas at worst they can be fatal. On some occasions, potential risks can also prevent IVN use when otherwise it would be indicated. Close clinical supervision and adequate monitoring are the only way to ensure early detection of problems in order to limit risks. All staff dealing with IVN patients must therefore understand IVN-related complications and teaching other staff to recognise the problems is an essential role for nutrition teams.

Complications of intravenous catheter insertion

Insertion of catheters for IVN (see Chapter 3) carries some immediate risk. This is dependent on the type of line involved, the skill of the professional placing it and the clinical condition of the patient. Most IVN catheters are placed using a Seldinger technique with a strict aseptic protocol to minimise infective risks (Figure 12.1).

It is often possible to place short-term IVN catheters on hospital wards but those for longer-term use, e.g. tunnelled lines, are usually placed in operating theatres. Patients with poor veins may also require line placement in theatre with Doppler vein imaging and/or cutdown techniques. Very difficult access is often best left to interventional radiologists.

The placement of central lines in subclavian or internal jugular veins carries more risk than peripheral catheter placement. Problems with arterial puncture, bleeding, pneumothorax and malposition can occur. Arterial puncture is usually obvious at the time of line insertion due to the high pressure and the presence of ‘artery-red’, pulsatile blood in the catheter. Nevertheless, there have been cases of IVN administration into arteries, which can cause limb discomfort if infused into a

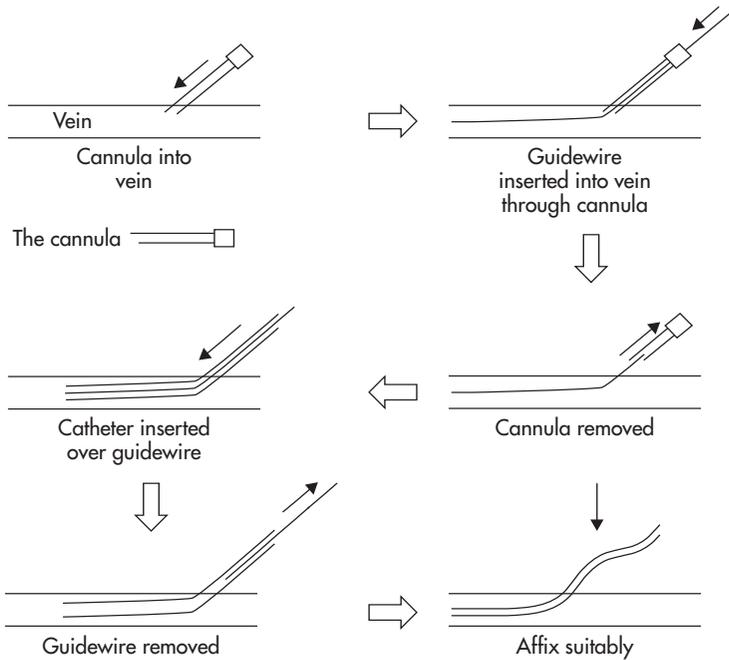


Figure 12.1 Intravenous line insertion using a Seldinger technique.

subclavian vessel and focal neurological symptoms or signs if infused into a carotid artery.

Placement of both subclavian and internal jugular catheters risks local bleeding. If the source of blood loss is the jugular vein, it is usually obvious and relatively easy to staunch with local pressure. However, bleeding from the subclavian may be unseen and not so easy to stop. The jugular approach is therefore favoured if the patient has any clotting abnormality.

Risks of accidental pneumothorax are also greater with subclavian insertions compared with internal jugular placements and, if an accidental pneumothorax would pose a very high risk for a patient, the subclavian route should be avoided (or only used with radiological or Doppler guidance). A chest X-ray is needed in all patients after upper-body central catheter placement to exclude a pneumothorax and to confirm the position of the catheter tip (see below). In order to avoid the serious dangers of bilateral pneumothoraces, a failed subclavian placement should be followed by X-ray exclusion of a pneumothorax *before* attempting the subclavian approach on the other side. Rarely,

pneumothoraces are accompanied by significant surgical emphysema, with air under the skin causing swelling of the upper torso, neck or face. This crackles under the fingers when touched. Air embolus can also occur with central line or peripherally inserted central catheter (PICC) placement, since the high blood flow in central vessels can pull significant quantities of air into the circulation if the catheter is accidentally left open to the atmosphere.

Postplacement chest X-ray of a central catheter is also needed to confirm the position of the line tip. Routine placement of any central catheters without imaging cannot guarantee that the tip is in the correct position and problems such as cardiac arrhythmias arise if the line is in too far. Conversely, there is an increased risk of large-vein thrombosis if it is not in far enough. The catheter tip can also end up in the wrong vein, e.g. going up into the cerebral venous drainage rather than down towards the heart. Chest X-ray confirmation should be clearly documented by a clinician before the line is used. X-ray confirmation of correct tip position is not required for femoral lines.

If the line has been inserted too far, aseptic withdrawal is acceptable. However, if the catheter has not been inserted far enough, pushing it in further is not permissible since this may introduce infection from micro-organisms contaminating the catheter surface. Nevertheless, you can try to replace a line that is not in far enough by railroading a new one into the vein over a sterile guidewire placed through the original, badly positioned line before removal. A repeat chest-X ray is then required.

Complications from peripheral insertion of midline feeding catheters or peripheral feeding cannulae are usually local and minor. Placement should still use aseptic techniques and success is very dependent on the condition of the patient's veins. Midlines and peripheral cannulae do not need confirmation of correct placement prior to use, whereas PICC lines need to be treated the same as other central catheters.

Infective complications from intravenous nutrition

Catheter-related sepsis (CRS) is one of the commonest complications of IVN and reduction in CRS rates is a key goal for nutrition teams (see Chapter 14). CRS usually occurs from blood-borne bacterial infections following infection of an internal lumen of the feeding catheter from poor aseptic technique during catheter access. All catheter use should

therefore be minimised and strict aseptic protocols must be used whenever the catheter is accessed for IVN, drug administration or blood sampling. Occasionally, a catheter is contaminated during insertion and skin infections at catheter exit sites can also track down to the blood stream.

CRS causes several symptoms and signs (Box 12.1) but it is often difficult to know whether a patient with apparent CRS problems actually has another source of infection. If the patient is obviously septic, investigations will be needed to determine the source. This requires various samples to be sent for culture, including urine, blood and, if appropriate, sputum or wound swabs. Imaging, for example, a chest X-ray or abdominal computerised tomography (CT), may also be required to exclude pneumonia or intra-abdominal collections. However, while results are pending, 'blind' treatment can be started to cover the most likely cause of infection.

Since IVN is an ideal growth medium for many micro-organisms, it is inappropriate to infuse feed through an infected line until the infection is at least controlled, if not eradicated, and all IVN should be discontinued whenever CRS is suspected. Resolution of pyrexia on cessation of feeding increases the likelihood that CRS was the problem. Carefully labelled (e.g. 'white lumen') blood cultures should be taken in all cases from each lumen, ideally with simultaneous peripheral blood cultures. Results take up to 48 hours to return and CRS is only unequivocally confirmed if a blood culture taken through one of the catheter lumens is not only positive but yields a colony count 1000 times greater than that from a simultaneous peripheral blood culture. If both peripheral and catheter cultures are not available, it is more difficult to be certain of CRS. A positive lumen culture with negative peripheral cultures suggests CRS is the problem but may be caused by sample

Box 12.1 Common signs of sepsis

General clinical deterioration
Rigors
Raised temperature $\geq 38^{\circ}\text{C}$
Low temperature $\leq 36^{\circ}\text{C}$
Raised pulse rate
Raised respiratory rate
Raised white cell count (occasionally low white count)
Raised inflammatory markers, e.g. C-reactive protein

contamination. A positive peripheral culture with either negative catheter cultures or catheter cultures with a similar colony count to that obtained peripherally suggests a non-catheter source of sepsis.

If CRS is not thought to be the likely cause of infection in an IVN patient, the line may still be used for feeding subject to regular review. If CRS is thought to be the problem in a short-term line, it should usually be removed and the tip sent for culture (the exit site must be disinfected before removal). Antibiotic treatment can then be given if necessary and the line replaced if needed once antibiotics are circulating. However, there is some risk of sepsis ‘seeding’ to a new catheter. Its use for IVN should therefore be avoided if possible until antibiotics have been given for 24–48 hours and appear to have been effective. Ideally, it is best to defer replacement of a catheter removed for suspected sepsis for this period if possible.

If CRS is suspected in a line needed for long-term access (e.g. a tunnelled line) or replacement of a short-term line would be very difficult or impractical, you can try to salvage the catheter from infection. When this is necessary, IVN should still be stopped and antibiotics commenced, usually beginning with ‘blind’ therapy (Box 12.2) and later modified following blood culture results.

If antibiotics are used to try to salvage an infected central line with more than one lumen, they should be given via alternate lumens for each dose. The last part of each dose should then be locked into the lumen until it is to be used again. This will discourage septic seeding between lumens. Some centres also use specific concentrated line locks for treatment of CRS, aiming for higher antimicrobial concentrations and so better clearance rates. We do not recommend this approach since the

Box 12.2 Typical ‘blind’ treatment of suspected intravenous nutrition line sepsis

Likely micro-organism:

Staphylococcus aureus (from skin)

Drugs of choice (in order of preference, depending on allergies and local policy):

1. Flucloxacillin (avoid, as there is a risk of methicillin-resistant *Staphylococcus aureus*)
2. Vancomycin
3. Teicoplanin
4. Linezolid

concentrations in the catheter achieved with conventional doses far exceed minimum inhibitory concentrations and it is important to ensure that the antibiotic is given in a volume that will permit adequate treatment of blood-borne infection.

Infected IVN catheters left in place for attempted salvage can, if absolutely necessary, be used for intravenous fluids and drugs, although this makes it difficult to lock antibiotics into the lumen(s). Furthermore, if absolutely necessary, a previously infected short-term line can also be used to recommence IVN if sepsis has been controlled for 24–48 hours by appropriate antibiotics which are going to be continued to complete a full treatment course. However, this practice will make complete clearance of a line infection less likely and hence should be avoided whenever attempting to salvage an infected long-term catheter (i.e. no IVN should be given during antimicrobial treatment for suspected or confirmed CRS in a long-term IVN line). It is also important that if any patient shows signs of worsening or renewed sepsis when recommencing IVN, it is immediately stopped and further cultures sent as above.

Other measures to help clear infection from long-term catheters include drugs to dissolve lipid or fibrinaceous deposits in which infection can persist (see below). Eradication of fungal line infections is particularly difficult and any use of the line during attempted treatment is always inadvisable. Sepsis related to a peripheral feeding line should always prompt immediate cessation of IVN and removal of the midline/cannula with the midline tips sent for culture.

Prophylaxis against internal lumen sepsis

The administration of antibiotics down a previously used line lumen to prepare it for IVN is unlikely to be effective and there is a risk of promoting bacterial resistance. Patients receiving long-term IVN as an intermittent infusion who have repeated CRS episodes may benefit from the use of prophylactic intravenous taurolidine. This is usually locked into the line lumen as a 2% solution after completing a feed and then flushed through before the next bag of IVN is commenced¹.

Occlusive catheter complications

Occlusion of a catheter prevents its use and the break-up of any solid material can risk embolisation, vein blockage and thrombosis. Occlusion results from a range of factors, shown in Box 12.3.

Box 12.3 Potential causes of intravenous catheter occlusion*Mechanical obstruction*

- Closed clamp
- Kink in line
- Line tip against vein wall

Pharmacological incompatibility

- Intravenous nutrition instability
- Drug–drug precipitate
- Drug–nutrient precipitate

Deposition

- Lipid

Thrombosis

- In the central veins
- In the line lumen
- At the line tip

Whenever a catheter seems to be blocked, you should first check that there is no obvious mechanical obstruction such as a kinked line or closed tap. Establishing that the catheter tip is lying against the vein wall is difficult but is likely if repositioning of the patient allows free catheter flow. Imaging may be needed to confirm your suspicions.

If you think that the lumen itself is blocked, consider whether any therapies that could cause precipitation have been given. Any drug that is incompatible with cations such as magnesium or calcium, for example ciprofloxacin, will also be incompatible with IVN, and many other drugs can cause precipitation problems, e.g. aciclovir². Sodium and/or fluid may destabilise the lipid in IVN and lipid deposition should be suspected if intravenous fluids, with or without electrolytes, have been run simultaneously with the IVN through the same lumen (see Appendix 1). Administration of blood or blood products with IVN should always be avoided for, although IVN is administered into the blood stream, there is inevitable uncertainty about its compatibility with non-blood components of blood products. Concentrations of electrolytes will also be much higher when the IVN and blood product mix within the catheter lumen compared to their mixing within a rapidly flowing vein. The same reasoning means that you should avoid putting incompatible therapies down the same lumen using devices such as a three-way tap or a side-infusion through a giving-set port, while you can allow them to be given down separate but adjacent lumens in

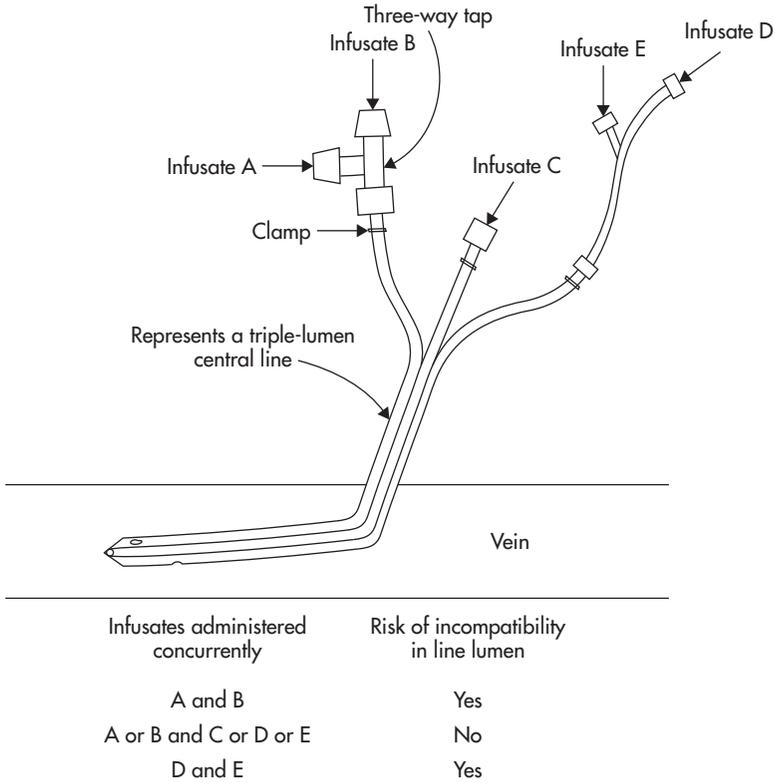


Figure 12.2 Risk of interaction of infusates used concurrently through the same intravenous line.

a central line, since rapid dilution will occur within the blood stream (Figure 12.2).

During prolonged IVN, lipid deposition can occur on the internal surface of catheters and this can also cause complete occlusion. Similarly, thrombosis can block catheters, especially if there has been any stagnation. Lines should therefore be flushed and locked between use and once-weekly alcohol locks to dissolve any lipid deposits should be considered in long-term IVN patients (see below).

Even when no stagnation occurs, fibrin clots can form on the line tip. These may cause a ‘trapdoor’ effect, allowing the line to be flushed through with ease but making it difficult to draw back blood (Figure 12.3).

Fibrin deposits on line tips can also extend to form large clots, which may occlude the vein and even embolise. It is therefore important

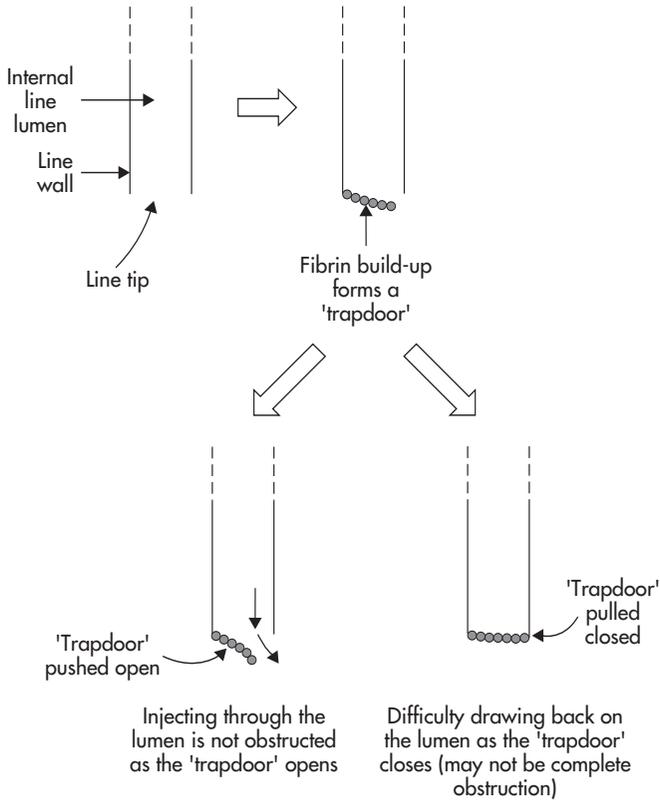


Figure 12.3 Fibrin clot 'trapdoor' effect at the tip of an intravenous catheter.

to recognise signs of a developing problem such as difficulty drawing back on the line or partial obstruction. A large cuff of clot may also form around the line as it lies within a vein and if this is suspected, e.g. from arm swelling on the same side as a subclavian catheter, anticoagulation should be commenced immediately unless there is a major contraindication. Short-term lines should be removed, although in doing so there will be a small risk of precipitating a pulmonary embolus. With long-term lines, it may be appropriate to see whether the clot resolves with anticoagulation or even to use fibrinolytics. Venography may be needed to establish the extent and level of threat from a clotting problem and clearly, in some patients, the first recognition of a line-related clot will be a pulmonary embolus.

Prophylaxis against line occlusion

Prevention of catheter occlusion is clearly better than trying to clear an established blockage. Catheters should always be flushed before locking the line to limit any potential for coagulation. If, in order to prevent blood sample contamination, it is necessary to leave the IVN static in a lumen for a short period while the sample is taken from a different lumen, a flush should be given immediately after to all other lumens of the same line (never disconnect and reconnect an IVN bag). If an IVN bag runs out before the next one is available, it should be taken down promptly and the lumen flushed (see Chapter 16).

Several measures, related to the potential causes of line blockage (Box 12.3), can be helpful:

- Always manipulate and secure the line carefully
- Dedicate a lumen for IVN whenever possible
- Always be sure of compatibility before putting any other infusate through a catheter lumen at the same time as IVN (Figure 12.2; see Chapter 3 and Appendix 1)
- Always flush the lumen before a new IVN bag and between each IVN bag and each and every drug
- Do not leave IVN or blood products static in the lumen
- Use a push-pause technique to achieve greater turbulence within the lumen when flushing lines³
- Always report any stiffness in drawing back on a lumen – to detect tip thrombosis as early as possible
- Always report chest pain in the patient to a clinician since this may be due to vein thrombosis and embolisation

Catheter occlusion is a significant problem in patients on long-term home IVN, especially as many receive overnight infusions with the line left unused during the day⁴. A number of additional measures may be helpful in such patients:

- Heparin ‘locking’ of the IVN catheter during the day is advocated by some centres but is of uncertain effectiveness⁴
- Addition of heparin into IVN regimens⁴ is used by some centres but may also be ineffective and may cause stability problems (Appendix 1, Box A1.4) whilst increasing bleeding risks
- Prophylactic alcohol locks are used by some centres to limit lipid deposition (Box 12.4)

Box 12.4 Prophylactic alcohol line locking*Indication*

Limiting lumen lipid deposits where the patient receives long-term intravenous nutrition lipid

Method

Once-weekly instillation of 80% alcohol into the line lumen, left for 5 minutes before withdrawal. The volume instilled should be the volume of the lumen (ask manufacturer) plus a very small excess

Preparing 80% alcohol from 100% alcohol (also called absolute ethanol or dehydrated alcohol BP)

Take 4 mL of 100% alcohol and *make up to* 5 mL with water for injection. More than 1 mL of water for injection will be required

Cautions

Patient taking metronidazole or particularly disulfiram. Any other circumstances where alcohol is cautioned or contraindicated

- Reduction in the duration of lipid infusion in patients on long-term IVN⁵
- Twice-weekly administration of lipids (see Chapter 10)

Management of catheter occlusion

If a catheter does become occluded, the management depends on the most likely cause of the blockage (Box 12.5 and Table 12.1).

Thrombophlebitis

Thrombophlebitis refers to inflammation of a vein wall. It can be painful, will predispose to thrombosis and can make a vein unusable in the future. Central vein thrombophlebitis is uncommon due to the dilutional effect of the fast blood flow but it may occur when the tip of the catheter rests directly on the vein wall. This causes both trauma and a high local concentration of infusate. It is usually manifest by central aching pain, made worse when IVN is being infused.

Peripheral vein thrombophlebitis (PVT) is relatively common with midlines and very common with peripheral cannulae. The use of peripheral cannulae for the administration of IVN is therefore discouraged

Box 12.5 Management options for central line occlusion, numbered in usual order of preference for suspected cases

Mechanical obstruction

- 1 Check line for kinks

Pharmaceutical instability

Soluble in acidic conditions (e.g. etoposide or heparin with amikacin or vancomycin⁶):

- 1 Acid

Soluble in alkaline conditions (e.g. phenytoin³):

- 1 Sodium bicarbonate

Lipid deposition

- 1 Alcohol
- 2 Acid
- 3 Fibrinolytic

Thrombosis

- 1 Fibrinolytic
- 2 Alcohol
- 3 Acid

Further details of management options can be found in Table 12.1

unless staff resources allow the cannula used to be swapped to a different vein after every IVN bag (see below). Signs of peripheral thrombophlebitis are shown in Box 12.6. Severe local damage related to thrombophlebitis can lead to tissue necrosis (Plate 4).

Box 12.6 Signs of peripheral vein thrombophlebitis

Local (i.e. same limb)

Erythema (redness)

Swelling

Inflammation

Pain

Soreness

Aching

Remember that the tip of a midline may be some distance from the apparent vein entry site

Table 12.1 Details of management options for central line occlusion*

<i>Management option</i>	<i>Details</i>	<i>Examples of variations and notes</i>
Acid	0.1 molar hydrochloric acid instilled into the lumen, left for up to 1 hour**, then withdrawn and repeated if necessary	0.1% hydrochloric acid ³ , 0.1 N hydrochloric acid ^{6,7}
Alcohol	80% alcohol instilled into the lumen, left for up to 1 hour**, then withdrawn and repeated if necessary	Other concentrations of alcohol may be recommended – 70% ^{3,7} or 90% ⁴
Fibrinolytic	Urokinase 5000 units per mL ^{6,3,8} or Streptokinase 250 units per mL ⁸ instilled into the lumen, left for 1 hour**, then withdrawn and repeated if necessary	Avoid use of streptokinase; consider alteplase first. Adverse effects are more likely with streptokinase than with urokinase ^{3,8} and there is a risk of sensitisation and ineffectiveness if previously treated with streptokinase. The recommended urokinase dwell time may vary – 5–10 minutes ⁸ , 30–60 minutes ³ , 2 hours ⁶ . The use of an infusion ^{4,9} is not recommended due to the risks of forcing solid material into the vein and rupturing the line. Forcing the catheter lumen may cause rupture ¹⁰ and this may force solid material into the vein
Sodium bicarbonate	1 mEq/ml sodium bicarbonate instilled into the lumen, left for up to 1 hour**, then withdrawn and repeated if necessary	Do not use with intravenous nutrition precipitation because calcium and phosphate solubility is pH-dependent ⁶ , being higher at low pH and adding more bicarbonate increases the pH, which is likely to lead to further precipitation/solidification ⁶

* Note that for all lumen instillations the volume instilled should be the volume of the lumen (ask manufacturer) plus a very small excess.

** Check compatibility with line manufacturer and refer to local guide lines.

Table 12.2 Risk factors for intravenous nutrition (IVN)-related thrombophlebitis

<i>Risk factor</i>	<i>Reasons</i>
Small vein diameter	Small veins have low blood flow and hence there is relatively less dilution of the hypertonic IVN ^{11,12}
External diameter of intravenous catheter	Small intravenous catheters permit higher rates of blood flow around them and hence greater dilution of administered IVN ¹¹ . They are also less likely to cause direct irritation of vein walls
IVN concentration	Higher IVN concentrations are more likely to cause tonicity-related damage to cells lining the veins
Inherent venous irritability of IVN components	Potassium is an example of a component that is inherently irritant to veins
Condition of veins	Frail and elderly patients often have less patent veins with lower tolerance to vein trauma. Veins recently used for previous venepuncture or fluid administration may have some existing damage, predisposing to thrombophlebitis
Duration of IVN administration	The longer a vein is used, the more likely that irritation and damage will occur

A variety of risk factors predispose to the development of PVT (Table 12.2).

Prophylaxis against peripheral vein thrombophlebitis

Several measures may help to reduce the incidence or severity of PVT (Box 12.7), although the success of pharmacological prophylaxis against PVT is probably limited¹⁶. The use of multiple techniques may offer benefit when giving IVN via a midline¹⁷ although, in our and other's experience, midline IVN is often well tolerated anyway, even if using IVN osmolalities usually intended for central rather than peripheral administration¹⁸.

Some groups have also reported success using peripheral cannulae for IVN with no pharmacological interventions other than low regimen osmolality, as long as the IVN is administered as an intermittent infusion for 12 hours in 24, removing and replacing the cannula in the opposite arm (avoiding the antecubital veins) for each bag¹⁴. However, the use of this technique requires impeccable cannula care and considerable

Box 12.7 Potential measures to help prevent peripheral vein thrombophlebitis

Addition of hydrocortisone and/or heparin to the intravenous nutrition (IVN) regimen

Topical 5 mg glyceryl trinitrate patch

Topical non-steroidal anti-inflammatory drug to appropriate limb¹³

Limiting duration of IVN administration through a peripheral cannula before replacement^{14,15}

Using a midline rather than a peripheral cannula

Limiting concentration of IVN regimens (do not use lipid-free regimens peripherally due to the high osmolality of the glucose). This may require a significant compromise on nitrogen and energy provision

Always ensure adequate stability data before adding anything to an IVN regimen (e.g. the addition of hydrocortisone and heparin to regimens may cause problems¹¹)

resources to ensure prompt resiting of the cannulas. Repeated cannula replacement is also painful for patients¹⁵.

Plate 4 shows unexpected tissue necrosis as a result of a peripheral micronutrient infusion through a cannula – a warning of the consequences of using too high a concentration in too small a vein.

Management of peripheral vein thrombophlebitis

When PVT is suspected, IVN should be discontinued and the catheter removed. The tip of the line (excluding peripheral cannulae) should then be sent for culture. Persistent pain caused by PVT may be helped by the topical application of a corticosteroid (e.g. 1% w/w hydrocortisone) to the affected site.

Microparticulate risks of intravenous nutrition and in-line filtration

An in-line filter (attached to the IVN giving set) acts as a sieve, preventing any contaminants larger than the filter pore size entering the patient's vein (Box 12.8). The use of such filters is recommended by some authorities with a view to reducing a number of potential problems, including the incidence of PVT. However, the use of filters, although

Box 12.8 Examples of potential intravenous nutrition contaminants removed by in-line filtration

Particulates shed from the internal surfaces of the bag and giving set
Glass particles introduced from bag additions from glass ampoules
Precipitates in case of compounding errors or inappropriate bag storage
Large lipid globules from 'creaming' (see Appendix 1) or bulk lipid infusions
Microbiological contaminants such as fungi or endotoxins

Note

Contaminant retention depends on the specific filter characteristics, e.g. the pore size used. For regimens with lipid this is 1.2 micron to allow the lipid globules through. For lipid-free regimens it is 0.2 micron. Other filter characteristics can include charged coatings which aid retention of endotoxins and allow longer use of the filter (refer to manufacturer's recommendations and local policy)

desirable, comes at a significant cost and, although the intravenous infusion of any large pieces of solid material is a definite risk for problems such as pulmonary embolus, it is more difficult to provide evidence that limiting infusion of the tiny particulates shown in Box 12.8 grants significant advantages. Furthermore, most short-term IVN patients are likely to receive many other infusions without in-line filtration, all of which pose the same potential problem of microparticulate infusion. Retention of fungi, the other proposed argument for in-line filters, is also unlikely to be an issue given that IVN compounding facilities (see Chapter 15) are designed to prevent microbiological contamination of prepared bags. These facilities should also routinely filter injections drawn from glass ampoules to limit glass particles. We therefore recommend that the use of in-line filtration is reserved for patients on long-term IVN (plus infants and small children), although such advice does add a risk management aspect to the IVN service.

If an appropriately sized filter is being used and it blocks, it should never be removed to continue the infusion. This is because the blockage must be assumed to be due to clogging with contaminants that have been prevented from entering the patient's veins. Stop and disconnect the IVN infusion and seek specialist advice from the nutrition team or Technical Services (see Chapter 15).

Metabolic complications of intravenous nutrition

Metabolic complications of IVN usually result from inadequate, excessive or unbalanced provision of individual IVN components (see Chapters 7–10). The most common metabolic problem is hyperglycaemia, whereas the most dangerous is the refeeding syndrome (see Chapters 8 and 9). Allergic reactions to the lipid component of IVN have also been reported but are rare¹⁹.

Complications related to fluid

Fluid overload, especially with saline, can result in oedema, congestive cardiac failure and worsening ascites. It can also precipitate partial ileus or delay the recovery of gut function following abdominal surgery. It may therefore contribute to the original need for IVN and then prolong that need. Overload with hypotonic fluids can also cause dilution of plasma with widespread effects, including cardiorespiratory compromise, hyponatraemia, confusion and even coma. Fluid deficiency results in dehydration with multiple potential consequences. These include reduced blood pressure and cardiac output, concentration of serum electrolytes with pseudohypernatraemia, nausea, vomiting, confusion, coma and renal failure. More details of these fluid-related problems are given in Chapters 7 and 10.

Excessive or inadequate provision of amino acids

Excess provision of amino acids is not usually considered harmful and, within limits, may improve nitrogen balance. As discussed in Chapter 7, however, the pattern of amino acids provided by IVN may not be fully utilised by sick patients who need an unusual pattern to meet the demands of their acute-phase response. High levels of amino acid provision may therefore produce metabolic upset (see Chapter 7) and will also result in increased urea production that will need to be cleared by the kidneys (see Chapter 10).

Inadequate provision of amino acids will result in excessive lean tissue loss.

Excessive or inadequate provision of carbohydrate

High levels of glucose provision cause hyperglycaemia, not only in previously diabetic patients, but also in many seriously ill or injured

patients who are frequently insulin-resistant. This can have several serious consequences, including:

- Increased risk of sepsis
- Increased risk of rebound hypoglycaemia on stopping IVN
- Higher probability of refeeding syndrome
- Diabetic ketoacidosis
- Increased carbon dioxide production (see Chapter 10)
- When administering IVN through peripheral veins, an increased risk of thrombophlebitis
- Abnormal liver function

Inadequate provision of glucose in IVN may result in hypoglycaemia and a low total calorific intake will cause weight loss as well as limiting the capacity to utilise amino acids in the IVN for protein manufacture. Prescribing IVN for diabetics or those patients with insulin resistance is considered in Chapter 10.

Excessive or inadequate provision of lipid

Excessive provision of lipids in IVN can result in respiratory compromise and coagulopathies²⁰. In the long term, it may also cause liver damage (see below) and could be a risk for atheroma. The respiratory compromise from excess lipid includes both an increased infective risk due to lipid accumulation in macrophages, especially in the lung, and the problems of increased oxygen demands due to the greater need for oxygen when metabolising lipid compared to glucose for the same amount of energy production (see Chapter 10).

Inadequate lipid provision in IVN can result in low total energy provision and hence weight loss. In the longer term it may also lead to deficiency of essential fatty acids, including ω_6 -linoleic acid and ω_3 -linolenic acids needed for membrane function and immune/inflammatory responses (see Chapter 7). Inadequate lipid energy also increases the osmolality of the IVN due to the additional glucose and hence the risk of thrombophlebitis if administered into a peripheral vein (see above and Chapter 7).

Excessive or inadequate provision of electrolytes

Abnormalities in plasma or tissue electrolyte levels may cause severe problems (see Chapter 8) and disturbances of sodium, potassium, calcium, magnesium and phosphate are frequently seen in IVN patients.

They are particularly common during the early stage of IVN when changes in whole-body electrolyte content due to the effects of malnourishment are coupled with the problems of abnormal electrolyte regulation, provision and loss that are so common in intestinal failure patients. They are also integral to the threat from refeeding syndrome which puts patients at grave risk (see Chapter 8).

Excessive or inadequate provision of micronutrients

Excessive or inadequate provision of micronutrients can result in the toxicity or deficiency problems described in Chapter 9. The development of Wernicke–Korsakoff syndrome with refeeding is a particular danger. There may also be interactions with other therapies, for example excessive vitamin K administration can result in difficulties obtaining a therapeutic international normalised ratio (INR) for patients requiring warfarin.

Liver function abnormalities

IVN can lead to both acute and long-term abnormalities in liver function. In the acute setting, it may be difficult to determine whether a liver problem is IVN-induced or whether it is due to other aspects of the patient's illness, including:

- Portal bacterial translocation (e.g. in hepatobiliary or pancreatic surgery patients and patients with intra-abdominal infection or small-bowel overgrowth)
- Sepsis from any source
- Biliary obstruction of any cause, e.g. retained stone
- Unrecognised previous chronic liver disease (e.g. long-term alcohol-related liver damage)
- New liver disease (e.g. drug reaction, infective hepatitis or liver abscess)

IVN patients with liver function abnormalities may therefore need imaging of the liver (usually starting with an ultrasound), blood tests for other causes of liver disease and a careful review of drug charts to check for possible side-effects from other drug therapy.

Most early (< 3 weeks) changes in liver function that are due to IVN are usually a consequence of steatosis (fatty liver). This usually causes a modest rise in level of alanine or aspartate transaminase (see Chapter 13). The abnormalities tend to occur in the first few days or

weeks of IVN, especially if there is excess glucose provision and the patient has previously been very malnourished. There is usually little or no disturbance in liver synthetic function and the changes are generally of little concern²¹.

The liver complications of longer-term IVN tend to be predominantly cholestatic (see Chapters 10 and 13). These usually occur several weeks or months into intravenous feeding and initially cause increases in alkaline phosphatase levels. Later there may be rising bilirubin and transaminase levels with significant impairment of liver synthetic function. The latter is best monitored by measuring INR. If unchecked, long-term IVN liver damage can occur with progress to cirrhosis and liver failure. It is particularly seen in home IVN patients who have been fed for several years (see Chapter 13).

Intrahepatic cholestasis is the commonest problem underlying the IVN-induced cholestatic changes and particularly occurs with overprovision of lipid. It can occur, however, with quite modest feeding levels in vulnerable individuals. The cause is unclear but may relate to the loss of neurohumoral signalling from the gastrointestinal tract to the liver, such as the absence of the normal cholecystokinin release triggered by meals. Cholestatic problems are particularly common in patients with a very short bowel and high stomal losses, possibly due to the high loss of bile salts from the stoma which leads to reduced bile solubility. Actual biliary sludging, acalculous cholecystitis, gallbladder dilatation and gallstones can occur in any long-term IVN patient, especially with excessive energy intake from glucose or lipid. These may result in significant biliary obstruction and hence further increase the risks of cirrhosis. Abnormal levels of bacterial translocation from a damaged gut via the portal system may also play a role in causing liver damage in some patients and it is worth trying a course of antibiotics (e.g. ciprofloxacin with metronidazole) likely to be active against a broad range of gastrointestinal organisms.

Management of IVN-induced liver dysfunction

If, after other potential causes have been excluded, the most likely cause of liver dysfunction appears to be the IVN, you will need to review and amend the prescription. A number of potential changes can be made but you will need to allow 10–14 days after each to determine whether they have led to any benefit. The following should be tried first:

- Review the patient's energy requirements (see Chapters 7 and 11) and, if lower than the total currently provided from *all routes*, reduce the IVN energy provision.
- Check that the ratio of glucose to lipid energy is as close to 50:50 as possible (see Chapter 7).
- Try intermittent IVN: gradually run the IVN regimen over a shorter duration using a higher rate, ultimately aiming to give over 12–16 hours with a significant physiological rest period (see Chapter 7).

If none of these measures helps, consider the following further options:

- Increase the relative glucose content – to give a glucose-to-lipid energy ratio of approximately 70:30. This type of regimen, with a high glucose content, will initially need to be given over 24 hours through a central vein with careful blood glucose monitoring.
- Switch to giving lipid in the IVN regimen on only 2 days per week, using glucose as the sole energy source on the remaining days.
- Change the type of lipid provided: different lipids may have less effect on the liver, although further evidence of this possibility is required (see Chapter 7).

In addition to the above measures, is also possible to consider oral ursodeoxycholic acid²², although further studies are required to prove its efficacy for this indication.

Conclusions

IVN complications are many, varied and can frequently occur with potentially fatal results. Prescribing from an office without a nutritional review of the patient is therefore always inappropriate and it is critical to ensure close clinical and laboratory monitoring of all IVN patients.

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