12. Complications

METHODS

Literature Search

Timeframe: 1990–2003 plus publications referred to in studies identified by search.

Type of publications: randomised controlled trials, cohort studies, case control studies and case series. Most studies were in adults.

Key Words: central venous thrombosis, child, compatibility, complication, drug interaction, growth retardation, infection, liver disease, metabolic disease, occlusion, parenteral nutrition, pulmonary embolism.

Language: English.

COMPLICATIONS OF PARENTERAL NUTRITION

Introduction

Complications may be considered in four groups: central venous catheter (CVC) related stability of the PN solutions and interactions with added drugs, metabolic or nutritional and other organ systems. CVC related complications include infection, occlusion, central venous thrombosis, pulmonary embolism and accidental removal or damage. Metabolic or nutritional complications include deficiency or excess of individual PN components including electrolytes, minerals, glucose, essential fatty acids, vitamins, trace elements and the presence of contaminants. Some of these are considered in the relevant chapters. Other organ systems may be affected by the PN solutions, the underlying disease process or both. Complications include hepatobiliary disease, metabolic bone disease and growth impairment, some of which may be life threatening and raise the need for other therapeutic interventions such as non-transplant surgery or small bowel and liver transplantation.

Complications of Central Venous Catheters

Infection

Infection is one of the commonest complications of CVC's and is potentially fatal. The emphasis should be on prevention by using an aseptic technique as detailed in the Venous Access chapter. PN fluids should be prepared in a suitable environment for aseptic compounding according to Good Pharmaceutical Manufacturing

Practice. Amino acid/glucose infusion giving sets and extensions can be left for 72 hours in-between changing ((1) (LOE 1); (2) (LOE 2); (3) (LOE 1)) but lipid sets should be changed every 24 hours ((4) (LOE 4)). Carers should be taught about the signs of catheter related sepsis (CRS) and monitor the child's temperature daily. Infection should be suspected if the child develops clinical sign such as fever (temperature >38.5°C or rise in temperature of >1°C) metabolic acidosis, thrombocytopenia or glucose instability. Blood cultures should be taken from the CVC ((5) (LOE 4); (6) (LOE 3); (7) (LOE 3)). Simultaneous peripheral blood cultures are generally only useful if a semi-quantitative or quantitative culture technique is used (e.g. pour plate blood cultures; time to positive on continuous monitoring blood culture systems). Commence broad spectrum intravenous antibiotics promptly. The choice of antibiotic must be based on local resistance patterns and changed to a narrower-spectrum therapy once the infecting microorganism(s) has/have been identified. The duration of therapy should be guided by the organism identified. Fungal CVC infection is an indication to remove the CVC. Persistent pyrexia with positive blood cultures after 48 hours of appropriate antibiotics may be an indication to remove the CVC. CVC infection rates should be regularly audited and prompt action taken if any increase is detected ((8) (LOE 4); (6) (LOE 3)).

Recommendations

- PN fluids should be prepared in a suitable environment for aseptic compounding according to Good Pharmaceutical Manufacturing Practice. **GOR D**
- Amino acid/glucose infusion sets & extensions should be changed after no more than 72 hours or as recommended by manufacturer. **GOR A**
- Lipid sets should be changed after no more than 24 hours or as recommended by manufacturer. **GOR B**
- Carers should be taught about the signs of catheter related sepsis (CRS). **GOR D**
- CVC blood cultures should be taken for any unexplained fever or other signs of CRS. **GOR D**

- Simultaneous peripheral blood cultures are generally only useful if a semi-quantitative or quantitative culture technique is used. **GOR D**
- For suspected CRS broad-spectrum IV antibiotics should be commenced promptly after taking CVC blood cultures, the choice of agents being based on local resistance patterns. Change to narrower-spectrum therapy should be practiced once the infecting microorganism(s) has/have been identified. The duration of therapy should be guided by the organism identified. **GOR D**
- CVC complication rates should be audited continually, any change should be investigated & appropriate action taken. **GOR D**

Occlusion

Occlusion of the CVC can originate within the CVC lumen (blood, drug or PN fluid precipitate), in the vein (clot or fibrin sheath), external to the CVC due to the tip resting against a vein wall or due to external compression e.g. clavicle, or patient positioning. Sodium chloride 0.9% should be used to flush the CVC between all therapies and blood sampling to help prevent precipitation ((9) (LOE 4)). When not in use, the CVC should be flushed at least once a week with heparin (see venous access chapter). The use of terminal in-line filters reduces the risk of debris entering the CVC and should be used for all PN fluids ((10) (LOE 4); (11) (LOE 4)). Occlusion of in-line filters should be investigated and the problem addressed, rather than just replacing the line and filter. Blood sampling increases the risk of occlusion due to fibrin deposition; it should be avoided if possible or at least kept to a minimum with careful planning. Any signs of leakage from the CVC, stiffness or increase in infusion pressures should be assessed and dealt with immediately by an experienced practitioner. If malposition or occlusion is suspected (e.g. inability to aspirate from catheter, increased infusion pressures) a chest X-ray should be performed to verify the catheter tip position ((12) (LOE 3); (13) (LOE 4)). CVC occlusion can be treated with: urokinase or alteplase for suspected blood deposits and ethyl alcohol or hydrochloric acid for suspected lipid or drug deposits ((14) (LOE 3); (15) (LOE 3); (16) (LOE 3); (17) (LOE 3); (12) (LOE 3); (18) (LOE 3); (13) (LOE 4); (19) (LOE 3); (9) (LOE 3); (20) (LOE 3)). A combination of more than one treatment may be required. Some manufacturers recommend that syringes smaller than 10 ml should not be routinely used to clear an obstruction as they can generate very high internal pressures (21). Unblocking the CVC with a guide-wire is not recommended. Catheter venography should be performed for persistent or recurrent occlusion ((12) (LOE 4); (13) (LOE 4); (22) (LOE 4)).

Recommendations

- Sodium chloride 0.9% should be used to flush the CVC between all therapies and heparin should be instilled at least weekly when the CVC is not in use. **GOR D**
- Terminal in-line filters should be used for all PN fluids. **GOR D**
- Occlusion of in-line filters should be investigated. **GOR D**
- Using the CVC for blood sampling should be avoided if possible. **GOR D**
- Leakage from the exit site, stiffness of the CVC or increased infusion pressures should be reported immediately to an experienced practitioner and appropriate investigations performed. **GOR D**
- CVC occlusion can be treated with: urokinase or alteplase for suspected blood deposits and ethyl alcohol or hydrochloric acid for suspected lipid or drug deposits. **GOR D**
- Syringes less than 10 ml should not be routinely used on CVC's. **GOR D**
- Unblocking the CVC with a guide-wire is not recommended. **GOR D**

Central Venous Thrombosis & Pulmonary Embolism

Central venous thrombosis (CVT) and pulmonary embolism (PE) are potentially fatal complications in children receiving prolonged PN. CVT tends to develop after several weeks of PN. It may result in facial swelling, prominent superficial veins or pain on commencing PN. CVT is confirmed by echocardiography, Doppler ultrasound, CT scan and/or venography ((23) (LOE 3); (24) (LOE 3), (25) (LOE 3); (26) (LOE 3); (27) (LOE 4); (28) (LOE 4)). PE may present with chest pain, dyspnoea, haemoptysis, syncope, tachypnoea, tachycardia, sweating and fever. Small thrombi may be asymptomatic or have vague symptoms such as tiredness.

CVT and PE are associated with recurrent CVC infection, repeated CVC changes, proximal location of the CVC tip in the superior vena cava, frequent blood sampling, concentrated glucose solutions, chemotherapeutic agents or may be idiopathic. Carers should look for any distress of the child, breathlessness, redness or swelling in the neck or limbs, leakage from the exit site or stiffness of the CVC on flushing and for any increase in pressure of the infusion pumps. These should be reported immediately to an experienced practitioner for assessment and action.

Acute symptomatic thrombosis may be best treated with thrombolytic agents but anticoagulation remains the most common therapeutic approach ((27) (LOE 4); (28) (LOE 4)). Consideration should be given to removing the

catheter, especially if infected ((29) (LOE 3); (5) (LOE 4); (28) (LOE 4)). Vitamin K antagonists ((30) (LOE 1/2); (31) (LOE 3)) or low molecular weight heparins ((32) (LOE 1/2)) may reduce the risk of thrombo-embolism and may be given to patients on long-term PN with previous or at increased risk of thrombo-embolism.

Recommendations

- Symptoms or signs of thrombo-embolism should be reported immediately to an experienced practitioner and appropriate investigations performed. **GOR D**
- Acute symptomatic thrombosis can be treated with thrombolytic agents or anticoagulation. **GOR D**
- Vitamin K antagonists or low molecular weight heparins may be given prophylactically to patients on long-term PN at risk of or with previous thrombo-embolism. **GOR B**

Accidental Removal or Damage

This can occur accidentally or deliberately by traction to the CVC. CVC's should be kept securely taped to the body to prevent excessive trauma to them, especially when not in use. Postoperative dressings should be secure, but allow observation of the exit site and be easily removable ((10) (LOE 4)). Dressings should stay in situ as per surgeons' instructions unless they become damp, soiled, loosened or there is swelling, bleeding and/or leakage from the CVC exit site and the dressing prevents observation. Tight vests, tape (trouser leg) splints or looping of the CVC can be used as extra security ((33) (LOE 4); (10) (LOE 4)).

Over time the integrity of long-term CVC's can be adversely affected and they may develop holes, tears or weakened connections. Some CVC manufacturers make repair kits and these can often be used to replace the damaged portion. Any damage to the CVC should be reported immediately to an experienced practitioner and appropriate repairs performed as soon as possible. Bleeding can occur from damaged CVC's or loose connections and is a potentially fatal complication. Luer lock connectors should be used to reduce the risk of disconnection and clamps should be available at all times to stop any bleeding. Children (as soon as they are aware) and all carers should be educated about the safety of the CVC ((33) (LOE 4); (10) (LOE 4)).

Recommendations

- CVC's should be securely taped to the body to prevent accidental removal, traction or damage. **GOR D**
- Postoperative dressings should be secure but allow observation of the exit site and easy dressing removal. **GOR D**
- Any damage to the CVC should be reported immediately to an experienced practitioner and appropriate repairs performed promptly. **GOR D**
- Luer lock connectors should be used to reduce the risk of accidental leakage and haemorrhage. **GOR D**
- Clamps should be available at all times to prevent bleeding from a damaged CVC. **GOR D**
- Children (as soon as they are aware) and all carers should be educated about the safety of the CVC. **GOR D**

Compatibility

The major issues affecting admixture stability were clearly set out by Barnett et al ((34) (LOE 4)). The use of organic-bound phosphates reduces the risk of precipitation. Addition of heparin to admixtures, even where validated, carries a small risk of emulsion instability occurring with individual batches of heparin ((35) (LOE 4)).

Parenteral nutrition in paediatrics can be admixed into '2 in 1' or '3 in 1' admixtures. A '2 in 1' admixture is one that contains amino acids, carbohydrates and electrolytes in a single container with lipid emulsion kept in a separate container. A '3 in 1' admixture has all the components including lipid in a single container. With up to 100 chemical species present in an admixture, enormous potential for interaction exists. It is recommended that a formulation is used that has been thoroughly studied in the laboratory and is backed by a clear statement from an authoritative body such as a licensed manufacturer or an academic institution, but there may still be variability through factors such as the variation in pH between different batches of glucose due to decomposition during autoclaving ((34) (LOE 4)) and changes in trace element profiles due to adsorption onto, or leaching from, admixture containers and tubing ((36) (LOE 3); (37) (LOE 3); (38) (LOE 3)). A '3 in 1' admixture is administered through a single line and the emulsion stability has been confirmed within the overall package. A '2 in 1' admixture validation generally excludes the lipid emulsion from any consideration during stability testing. The lipid emulsion is infused 'separately' but in practice this usually means into the same infusion line, through a 'Y' connector. This approach does not ensure stability (39,40 (LOE 3)). As there are risks associated with instability of regimens, it

has been recommended that PN admixtures be administered through a terminal filter ((41) (LOE 4)).

Recommendations

- PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution. **GOR D**
- A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives. **GOR D**
- Alternative ingredients should not be substituted without expert advice or repeat validation. **GOR D**
- Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation. **GOR D**
- If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to and occasional precipitates may still occur. **GOR D**
- Use of '2 in 1' admixtures with Y-site addition of lipids should be fully validated by the manufacturer or accredited laboratory or the lipid infused through an alternative line. **GOR D**
- PN admixtures should be administered through a terminal filter. **GOR D**

Drug Interactions

Interactions between PN and medications occur in three main ways; physiological interactions that occur at all times, altered behaviour of medications owing to the complications of the presenting condition or sub-optimal nutritional support and direct chemical interaction in the tubing during administration ((42) (LOE 4)).

Examples of the first type would be steroid-related hyperglycaemia or hypoglycaemia seen with concurrent insulin. These are predictable from the mode of action of the drug. In the second case, altered acid-base balance can lead to altered drug/receptor interactions or altered levels of protein binding, as can abnormal plasma albumin levels. It is difficult, for example, to reverse acidosis with bicarbonate if the patient is being overloaded with a non-metabolisable base such as chloride ((43) (LOE 4)). Similarly, if the patient is sodium depleted, diuretics will be ineffective. In neonatal jaundice bilirubin may be displaced from binding sites of plasma proteins by a number of medications, particularly sulphonamides, antimalarials and drugs containing benzoyl alcohol as a preservative ((44) (LOE 4)).

There are many short reports in the literature looking at the physical and/or chemical stability of certain medications in specific PN admixtures. Extrapolation of

these is difficult without expert advice. Medications are given in the form of a formulated product which frequently contains excipients (substances required for formulation of a drug which should be inactive) in addition to the active medication ((45) (LOE 4)). Studies must therefore be regarded as specific to the particular branded product(s) investigated. The pH of a PN admixture will generally be close to the pH of the amino acid mixture from which it was prepared ((34) (LOE 4)) but marketed products range from around pH 5.0 to pH 7.0. Drugs that ionise in aqueous solution are those most likely to cause precipitation. A drug that is largely unionised at pH 5.0 may be fully dissociated at pH 7.0 and *vice versa* so it is not possible to extrapolate findings between different admixtures.

The problem is further complicated because of the behaviour of fluids within infusion tubing, particularly at low flow rates. Sharp corners and hanging loops within the tubing can lead to 'non-circulating fluid spaces' where medications can pool, and not necessarily be cleared by flushing ((46) (LOE 4)). Adding medication into infusion sets can force a bolus of an equivalent volume of PN solution ahead of the medication. Also, depending upon where the drug is added to the set, it may delay delivery of all or part of the dose to the circulation if the dose volume is less than the residual volume of the tubing ((46) (LOE 4)). This means that any study of drug compatibility with PN can only be reliably applied to the particular products, concentrations, flow rates tested and the precise equipment, tubing, connectors and adaptors used. Extrapolation should only be attempted by those with relevant expertise. Problems will frequently manifest as in-line precipitation or lipid droplet enlargement (or both). In-line filtration can prevent these reaching the patient.

Recommendations

- Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory. **GOR D**
- Medications known to affect plasma protein binding of bilirubin should be avoided in parenterally fed newborn patients with severe hyperbilirubinaemia. **GOR D**

Refeeding Syndrome

The hormonal and metabolic changes of starvation aim to facilitate survival by a reduction in basal metabolic rate, conservation of protein, and prolongation of organ function, despite the preferential catabolism of skeletal muscle tissue and loss of visceral cell mass.

Refeeding the malnourished child disrupts the adaptive state of semi-starvation. Thus, refeeding syndrome may be observed in severely malnourished patients receiving concentrated calories via PN ((47) (LOE 4); (48) (LOE 4)). These rapid changes in metabolic status can

create life-threatening complications, so the nutritional regimen must be chosen wisely and monitored closely. To reduce the risk of refeeding complications, several conditions are required at the initial phase of re-nutrition of severely malnourished infants and children.

Prevention of Water and Sodium Overload

This can be achieved by:

- reducing water and sodium intake (some times up to 60% of the theoretical requirements), depending on the hydration state.
- monitoring to detect early fluid retention related excessive weight gain. It is preferable to maintain weight stable or even to achieve weight loss during the first 2–3 days of parenteral renutrition.
- preserving the oncotic pressure with the infusion of macromolecules such as albumin (1 g/kg at a slow infusion rate and if necessary twice a day).
- monitoring uncontrolled losses (skin and obligatory losses) as well as those from the gastrointestinal tract, intraperitoneal or intestinal fluid retention.

In clinical practice the early phase of renutrition requires monitoring at least once a day body weight changes, urine collection, assessment of blood and urinary electrolytes.

Carbohydrate Intake

Constant administration of carbohydrate is required to maintain blood glucose homeostasis as the reserves are very low; parenteral administration of glucose requires care because of the risk of hyperglycaemia with osmotic diuresis and hyperosmolar coma. According to age of the patient, continuous glucose infusion rate may be at least equal to the glucose production rate (see Carbohydrate chapter).

Potassium Repletion

Correction of potassium depletion should be achieved progressively with monitoring of renal and cardiac function. It can be dangerous to try to correct the deficiency too rapidly at a stage where the capacity for fixing potassium remains low because of low glucose intake and reduced protein mass and synthesis. At an early stage of re-nutrition; excessive potassium intake may cause hyperkalaemia and cardiac arrhythmias.

Phosphorus Repletion

Correction of phosphorus depletion should be achieved progressively with monitoring of neurological status and renal function. At least 0.5 mmol/kg per day should be administered and proportionally increased according to the total protein-energy intake up to 1.0 mmol/kg per day.

Daily monitoring of phosphoraemia and phosphaturia is mandatory, aiming at a limited phosphaturia.

Protein and Energy Intake

It is difficult to suppress protein catabolism in the early phase of re-nutrition since energy intake should be increased very slowly. Excessive nitrogen intake may lead to hyperammonaemia and/or metabolic acidosis by exceeding the renal clearance capacity for H+ and phosphate ions. An intake of 0.5–1 g/kg of parenteral amino acids or oral peptide is sufficient to maintain the plasma amino acid pool. The protein energy deficiency and other related disorders must be corrected during the days following the initial period of stress. This type of correction should be made carefully and gradually since the deficits are profound and of long standing. It is essential to provide both nitrogen and calories simultaneously and in the correct ratio (see chapter on amino acids).

Adaptation of Intake

The provision of appropriate nutrient solutions requires an understanding of the nutritional relationships between macronutrients, electrolytes, vitamins and trace elements. It is during this initial phase that any deficit due to incorrect intake will become apparent through either clinical or laboratory signs. These deficits can usually be prevented by giving them in the following proportions: 200 to 250 kcal, nitrogen 1 g, calcium 1.8 mmol, phosphorus 2.9 mmol, magnesium 1.0 mmol, potassium 10 mmol, sodium and chloride 7 mmol, zinc 1.2 mg. Similarly, it is essential to adapt the intake of essential fatty acids, copper, manganese, chromium, iron, iodine, cobalt, fluoride, selenium, tocopherol and the group B vitamins especially.

Monitoring

After the initial phase of re-nutrition, most complications may be prevented by careful supervision and the provision of appropriate intakes. It is essential that the infusion rate, body temperature, cardiac and respiratory function, urinary volume, twice daily weight and digestive output are continuously monitored. During the first 5 days, and also when the osmotic load is increased, urine should be checked for osmolality, pH, glucose and protein. The plasma and urinary ion data, plus the calcium, phosphorus, magnesium, glucose and haematocrits should be obtained twice during the first week, and then once weekly. Plasma proteins, albumin, bilirubin, alkaline phosphatase and transaminase values should be assessed routinely. This data, and knowledge of the patient's state and age, should make it possible to progressively regulate and control the intake and avoid problems of overload or depletion.

Prevention of Infection

The infective, metabolic and GI problems must be borne in mind during treatment of paediatric patients with severe malnutrition. The risk of infection, an expression of both specific and non-specific immunity depression, may jeopardize the prognosis and aggravate nutritional problems at any time. Clinical and para-clinical investigations must be performed repeatedly, to look for widening foci of infection (respiratory, GI, skeletal and urinary) and for their systemic spread. When a localized or systemic infection is identified, specific treatment is urgently required. The routine use of antibiotics in the absence of bacteriological evidence in a malnourished child is inadvisable; antibiotics should only be given if sufficient indirect evidence points to the likelihood of infection. Active intestinal parasitosis should be vigorously treated.

Metabolic Bone Disease

PN-related metabolic bone disease (MBD) with a decrease in bone mineral density (BMD), osteoporosis, pain and fractures has been described in adults on long-term parenteral nutrition. Little data exists in children, although its occurrence has been reported in children weaned from long-term PN ((49) (LOE 3); 50) (LOE 3); (51) (LOE 3)). The cause of MBD is probably multifactorial including both underlying disease and PN-related mechanisms: excess vitamin D, phosphorus, nitrogen and energy imbalance, excess amino acids and aluminium contamination ((52) (LOE 3)). Measurements of urinary calcium, plasma calcium, plasma phosphorus, plasma parathyroid hormone, vitamin D concentrations and serum alkaline phosphatase activity aid in the evaluation of MBD in patients on PN. Use of aluminium contaminated products should be kept to a minimum (avoid glass vials and certain minerals and trace elements known to have high aluminium content), and products with measured and labelled aluminium content preferred. Diagnosis of bone disease relies primarily on the measure of bone mineralization by validated imaging methods (e.g. peripheral quantitative computer tomography, dual energy X-ray absorptiometry).

Recommendations

- In children on HPN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and vitamin D concentrations and serum alkaline phosphatase activity should be performed. **GOR D**

- Aluminium contamination of parenteral nutrition solutions provided to patients receiving long-term PN should be kept to a minimum. **GOR D**
- Regular assessment of bone mineralisation should be performed. **GOR D**

Hepatobiliary Complications of Parenteral Nutrition

The liver and biliary tree have many essential roles including metabolism of carbohydrate and lipid; detoxification and elimination of endogenous and exogenous lipophilic compounds and heavy metals; and synthesis and secretion of albumin, bile acids, coagulation factors, cytokines and hormones. Most hepatobiliary complications of PN are moderate and reversible. In a few patients there may be more severe outcomes ranging from biliary sludge and gallstones to cirrhosis, hepatic decompensation and death.

The pathogenesis of PN associated liver disease is not completely understood ((53) (LOE 3); (54) (LOE 4)). It probably results from the interaction of many factors related to the underlying disease, infectious episodes and components of the PN solution. Elaborate discussion on the various approaches to the avoidance or treatment of the rare case of PN related hepatobiliary disease is discussed elsewhere ((55,56) (LOE 4)).

Patient and/or Disease Related Factors

Children requiring long-term PN are at high risk of developing liver disease. Absence of oral feeding impairs choleresis and increases the risk of biliary sludge formation. Short bowel syndrome may be associated with disruption of bile acid enterohepatic circulation due to ileal resection, bacterial overgrowth due to bowel obstruction or severe motility disorders and ileocaecal valve resection, which are all factors thought to contribute to PN-associated cholestasis ((57) (LOE 3), (58) (LOE 4)). Recurrent septic episodes either catheter-related (gram positive bacteria) or digestive related (gram negative sepsis from intraluminal bacterial overgrowth) also contribute to liver injury. Prematurity is an associated factor especially when necrotizing enterocolitis or septic infections occur ((59) (LOE 4)).

PN Related Factors

PN may have additional deleterious effects on the liver:

- It was experimentally demonstrated that an excess of total energy delivered induces liver lesions, reversible when decreasing the energy supply.
- Excessive or inadequate amino acid supply (60,61).

- Continuous PN infusion and/or excessive glucose intake is associated with hyperinsulinism and subsequent steatosis ((62) (LOE 3)), although it is not clear whether this is also associated with cholestatic liver disease.
- The role of inadequate lipid supply with excessive delivery of fat and subsequent lipoperoxidation has been suggested ((54) (LOE 4)). Phytosterols contained in lipid emulsions may be a marker for liver dysfunction ((63) (LOE 3); (64) (LOE 3)).

Monitoring

Careful monitoring of hepatic function is extremely important during PN in order to minimize or correct factors responsible for liver disease. The earliest and most sensitive, but not specific laboratory markers are plasma alkaline phosphatase and gamma-glutamyl transferase activities, while hyperbilirubinemia is the latest marker of cholestasis to appear. Clinical liver enlargement, confirmed by ultrasonography, may appear within a few days after PN onset. Liver biopsy is not indicated at the early stage of liver dysfunction. However, it was shown that steatosis is the first non specific histological abnormality resulting from excessive glucose supply leading to lipogenesis, rather than from the deposition of exogenous IVFE. Cholestasis together with portal and periportal cell infiltration leads to fibrosis. This indicates severe liver disease, with possible progression to cirrhosis and liver failure, unless digestive factors are corrected and PN is performed correctly.

Early referral to an experienced paediatric liver and intestinal transplant centre for further assessment is recommended in infants and children with a poor prognosis (e.g. ultra short bowel <10 cm, congenital enteropathy, megacystis microcolon and disorders of uncertain natural history. Clinical criteria include: parenteral nutrition >3 months, serum bilirubin >50 μmol/l, platelet count <100, PT > 15 sec, PTT > 40 sec or hepatic fibrosis ((65) (LOE 3)).

Prevention and Treatment of Cholestasis

Some measures may limit or reverse liver disease including:

- The stimulation of the entero-biliary axis by promoting oral feeding with breast milk or long-chain triglycerides containing formulae, or by injection of cholecystokinin analogues ((66) (LOE 3)).
- The reduction of intraluminal bacterial overgrowth caused by intestinal stasis by giving metronidazole ((67) (LOE 3)) and/or by performing venting enterostomy or tapering enteroplasty ((68) (LOE 4)).
- The use of ursodeoxycholic acid (10 to 30 mg/kg per day) or tauroursodeoxycholic acid might contribute in decreasing liver injury ((69) (LOE 3)).

Persistant Cholestasis

If cholestasis occurs in spite of the above preventive management, the clinician has to rule out biliary obstruction, infection or drug toxicity by using appropriate investigations. A decrease in platelet count below 150,000/mm^3 associated with an increase in plasma transaminases, may be suggestive of lipid toxicity when all other explanations are ruled out. Bone marrow aspiration and/or liver biopsy and temporary suspension or decrease in lipid infusion should be considered. If lipid infusion is stopped, essential fatty acid status should be monitored.

Recommendations

- Liver disease should be prevented by reducing patient-related and PN-related risk factors. **GOR D**
- Provide maximal tolerated EN even if minimal residual gut function. **GOR A**
- Commence cyclical PN as soon as possible. **GOR C**
- Consider and treat intraluminal bacterial overgrowth. **GOR D**
- Consider reducing or stopping IV lipids temporarily if conjugated bilirubin steadily increases with no other explanation. **GOR D**
- If the transaminases, alkaline phosphatase or conjugated bilirubin continue to increase consider commencing ursodeoxycholic acid. **GOR D**
- Early referral to an experienced paediatric liver and intestinal transplant centre for further assessment is recommended in infants/children with poor prognosis or if on PN for >3 months and serum bilirubin >50 μmol/l, platelet count <100, PT > 15 sec, PTT > 40 sec or hepatic fibrosis. **GOR D**

Growth Retardation

A child dependent on PN must receive adequate nutrition to meet its basic metabolic requirements but also to allow for normal growth ((70) (LOE 1)). This is particularly important in preterm infants who inevitably accumulate a significant nutrient deficit in the early weeks of life ((71) (LOE 3)) and may require aggressive nutritional support ((70) (LOE 1)). It is important to assess longitudinal growth as excessive weight gain with growth retardation has been described ((72) (LOE 3)). It has been suggested that the addition of ornithine a-ketoglutarate to the PN solution given to growth retarded children receiving home PN has an advantageous affect on growth as it provides key factors in both the Kreb's and the urea cycles ((73) (LOE 3)), but the efficacy of this approach has not been tested by other authors.

As a child's gut adapts and tolerates increasing enteral feeds, there is a temptation to cut back on PN days as soon as possible to ease the lifestyle constraints imposed

by PN. If the growth velocity slows when this is done, there may be a tendency to add the additional calories onto the reduced number of PN days rather than increasing PN days. This may lead to excessive weight gain without longitudinal growth ((74) (LOE 3)). Care must be taken in adjusting PN composition and amount frequently in line with growth ((74) (LOE 3)).

Parenteral nutrition is widely used in neonatal units to support preterm babies until enteral feeding can be established. The generally accepted goal is to provide adequate nutrition to allow for growth and weight gain as expected of a foetus of that post conceptional age ((75) (LOE 4)). The metabolic requirements of a sick preterm may be high and optimal intake is not always possible. Retrospective studies looking at the actual energy intake of preterm babies, rather than that prescribed have shown a significant deficit in relation to their requirements ((76) (LOE 3)). This deficit can be directly related to postnatal growth retardation. The use of insulin to maintain normoglycaemia rather than reducing glucose concentrations may have a beneficial effect on growth but may also have side effects ((77) (LOE 3)).

Recommendation

- Paediatric patients on long term PN require regular monitoring of growth and body composition. **GOR D**

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