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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Complications

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1. Methods

Literature search

Timeframe: publications from 2004 until December 2014 were reviewed

Type of publications: The search was restricted to infants and children (0–18 years) but not limited by publication form or language.

Key words: The search was conducted in Ovid Medline using both MeSH terms and text words for “parenteral nutrition

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complications". In parallel an expert search was conducted focusing on specific subtopics of parenteral nutrition complications.

Titles and abstracts retrieved by electronic and expert searches were first screened by a collaborator of Cochrane Hungary and clearly irrelevant abstracts were removed. Subsequently, members of the Working Group screened titles and abstracts for eligibility. Full texts of all potentially relevant manuscripts were retrieved and assessed.

damage; 2) admixture stability; 3) interactions between PN and medications; 4) metabolic bone disease; 5) hepatobiliary complications; and 6) effects of PN on growth parameters.

Other types of complications (e.g. metabolic or nutritional complications, Refeeding syndrome) are described in other chapters of this Guideline.

Table 14.1: Recommendations for the prevention of complications

R 14.1	Any child with IF and an indwelling CVC is at significant risk for CRBSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), or change in clinical or laboratory parameters should raise the suspicion of CLABSI until proven otherwise (LOE 2+, RG B, strong recommendation)
R 14.2	Paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein should ideally be obtained when a CRBSI is suspected and before the start of antibiotic therapy (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.3	The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP (differential time to diagnosis) between blood cultures drawn from the catheter and from a peripheral vein or separate lumen (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.4	Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.5	The duration of antimicrobial therapy for CRBSI with retained catheter is generally 10−14-days, assuming clinical and microbiological response within 48 −72 h and no evidence of complications (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation).
R 14.6	Removal of the CVC is recommended in the presence of clinical deterioration or persisting or relapsing bacteremia, presence of suppurative complications or for particular infectious agents (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.7	Thrombotic catheter occlusion and CVC related thrombosis require thorough investigation and treatment as they may be associated with significant morbidity (LOE 2−, RG B, strong recommendation)
R 14.8	Fibrinolytics are the drug class of choice for treating thrombus-occluded catheters. Tissue plasminogen activator (tPA, alteplase) is currently the recommended agent; however, urokinase and recombinant urokinase (rUK) can also be used (LOE 2+, RG B, strong recommendation)
R 14.9	The recommended management of acute and symptomatic CVC-related thrombosis depends on the requirement for the CVC and usually requires antithrombotic medication (LOE 2+, RG B, strong recommendation)
R 14.10	Proper positioning of the catheter tip and immediate investigation when catheter breakage or fluid extravasation are suspected should be implemented in order to prevent the occurrence of significant morbidity (LOE 4, RG 0, strong recommendation)
R 14.11	Appropriate measures to secure the catheter in place and education for users on correct maintenance and safety of the catheter are strongly recommended (GPP, strong recommendation
R 14.12	PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution (GPP, strong recommendation)
R 14.13	A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives (GPP, strong recommendation)
R 14.14	Alternative ingredients should not be substituted without expert advice or repeat validation (GPP, strong recommendation)
R 14.15	Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation (GPP, strong recommendation)
R 14.16	If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to (GPP, strong recommendation)
R 14.17	When '2 in 1' admixtures with Y-site lipids added are used, addition of lipids should be fully validated by the manufacturer or accredited laboratory, or the lipid infused through an alternative line (GPP, strong recommendation)
R 14.18	Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory (GPP, strong recommendation)
R 14.19	Multi-layer bags which are impermeable to oxygen are recommended for PN administration (GPP, strong recommendation)
R 14.20	Light protection is recommended for both PN bags and administration sets (LOE 3, RG 0, strong recommendation)
R 14.21	The recommended delivery site for PN is via a central line; however peripheral PN can also be given for short periods (LOE 3; RG 0, strong recommendation)
R 14.22	The osmolarity of peripheral PN solution should be kept less than 900 mosmol/l (LOE 3; RG 0, conditional recommendation)
R 14.23	In children on home PN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed (LOE 2+, RG B, strong recommendation)
R 14.24	Ingredients with the lowest amount of aluminum are advocated for the preparation of parenteral nutrition solutions provided to patients receiving PN (LOE 2++, RG B, strong recommendation)
R 14.25	Regular assessment of bone mineralization should be performed (LOE 2−, RG B, strong recommendation)
R 14.26	The risk of liver disease may be decreased by reducing patient-related and PN-related risk factors (LOE 2+, RG B, strong recommendation)
R 14.27	In patients with intestinal failure-associated liver disease, maximizing enteral intake as tolerated may improve liver disease outcome (GPP, strong recommendation)
R 14.28	In patients on long-term and home PN, cyclic of PN infusion is recommended as soon as metabolic and fluid status allows (LOE 3, RG 0, strong recommendation)
R 14.29	Pure soybean-based lipid emulsions should be avoided in the presence of cholestasis (LOE 3, RG 0, strong recommendation)
R 14.30	The use of mixed LEs may be encouraged in IF patients for long term PN (LOE 3, RG 0, conditional recommendation)
R 14.31	The initiation of ursodeoxycholic acid may be considered in the presence of biochemical signs of cholestasis (LOE 3, RG 0, conditional recommendation)
R 14.32	Early referral to an experienced pediatric intestinal failure rehabilitation/transplantation centre is recommended in infants/children with intestinal failure-associated liver disease (GPP, strong recommendation)
R 14.33	All patients on long term PN require regular monitoring of growth and body composition (LOE 2−, RG B, strong recommendation)

2. Introduction

This chapter handles the following main areas where complications during parenteral nutrition may arise: 1) CVC related complications including infection, occlusion, central venous thrombosis, pulmonary embolism and accidental removal or

3. Complications of central venous catheters

3.1. Infections

Central line−associated bloodstream infections (CLABSIs) are the most common, serious complication associated with central

venous catheters (CVC) use. CLABSIs are a significant cause of morbidity and mortality in pediatric patients with intestinal failure (IF) who are parenteral nutrition (PN) dependent. Intravenous access is a lifeline for these patients, and the loss of vascular sites is an indication for intestinal transplantation [1,2] (LOE 2−). Furthermore, recurrent sepsis is also a major cause of IF-associated liver disease (IFALD) [3–5] (LOE 2−). Unless an alternative source is identified, all bloodstream infections in patients with a CVC are classified as CLABSI. When evidence confirms that the colonized device is the true source of infection, the more specific diagnosis of catheter related blood stream infection (CRBSI) is used [6] (LOE 2+).

The reported incidence of CRBSI in the pediatric literature is between 3.8 and 11.3 infections per 1000 catheter days, depending on patient and catheter variables [7] (LOE 2+). In children with IF the range of CRBSI is very similar, 1.2–10.2 ± 6.2 per 1000 catheter days [8–10] (LOE 3). The estimated reported frequency of CRBSI in home PN (HPN) patients in the literature varies between 0.34 and 3.94 episodes per catheter year [10–13] (LOE 3). Prevention focused protocols can reduce this rate to less than 1 per 1000 catheter-days [14] (LOE 2+). The major pathogens isolated are Gram-positive coagulase-negative (30–40%) or −positive (7.7–15%) staphylococci, Gram-negative bacteria (30–40%), fungi (4.6–6%) or polymicrobial flora (12%) [9,10,15] (LOE 3).

Risk factors that have been associated with an increased rate of CRBSI include prematurity, malignancy, previous abdominal surgery, small bowel length, presence of an enterostomy, lack of enteral nutrition, use of catheter for PN and duration of PN and use of antacids [16] (LOE 2+) [17]; (LOE 3) [18]; (LOE 2+). Medicard insurance and age <1 year were also associated with increased risk for CRBSI (odds ratio [OR], 4.4 [95% CI, 1.13–16.99] and 6.6 [1.50–28.49], respectively; $P < .05$) in children on HPN [19] (LOE 3).

3.1.1. Diagnosis of CRBSI

R 14.1	**Any child with IF and an indwelling CVC is at significant risk for CRBSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), or change in clinical or laboratory parameters should rise the suspicion of CLABSI until proven otherwise (LOE 2+; RG B, strong recommendation, strong consensus)**
R 14.2	**Paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein should ideally be obtained when a CRBSI is suspected and before the start of antibiotic therapy (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.3	**The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP (differential time to diagnosis) between blood cultures drawn from the catheter and from a peripheral vein or separate lumen (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**

Any child with IF and an indwelling CVC is at significant risk for CLABSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), lethargy, metabolic acidosis, hypoglycemia, thrombocytopenia or ileus in an IF patient must be presumed to be due to a CLABSI until proven otherwise [6,20] (LOE 2+). The US Center for Disease Control and Prevention has published guidelines for the diagnosis of CRBSI, mainly involving matching peripheral blood cultures with catheter blood or tip cultures [6,20]. However, few studies exist to validate these criteria in children and modified diagnostic criteria are often applied for practical purposes. A definitive diagnosis of a CVC-related infection can be challenging, especially in children. Standard qualitative peripheral blood culture remains the most commonly performed investigation for CRBSI, but does not indicate the source or quantity of organisms and is subject to contamination. In contrast, paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein represent a considerable improvement, and should be obtained before initiation of antimicrobial therapy [6,20] (LOE 2++ in adults).

Confirmatory tests for the diagnosis of CRBSI include: culture of the same organism from at least 1 percutaneous blood culture and from a culture of the catheter tip when the catheter is removed, or 2 positive blood samples, one from the CVC and the other from a peripheral vein, that meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP). For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI. The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP between blood cultures drawn from the catheter and from a peripheral vein or separate lumen. For DTP, growth of microbes from a blood sample drawn from a catheter hub at least 2 h before microbial growth is detected in a blood sample obtained from a peripheral vein best defines CRBSI [6,20] (LOE 2++ in adults). In a recent retrospective study in the NICU, optimal DTP cutoff for the diagnosis of CRBSI was >1 h, with a sensitivity of 94%, specificity of 71%, positive predictive value of 88%, and negative predictive value of 83%, suggesting that DTP of paired blood cultures may have some potential in the diagnosis of catheter related infections in this setting [21] (LOE 3). Cultures of blood from the catheter and when appropriate of soft tissues at the entrance-exit sites or tunnel should be obtained before the initiation of antibiotic therapy.

3.1.2. Therapy of CRBSI

R 14.4	**Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.5	**The duration of antimicrobial therapy for CRBSI with a retained catheter is generally 10–14-day, assuming clinical and microbiological response within 48–72 h and no evidence of complications (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.6	**Removal of the CVC is recommended in the presence of clinical deterioration or persisting or relapsing bacteremia, presence of suppurative complications or for particular agents (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**

In the 2009 update by the Infectious Diseases Society of America, the authors outline approaches to the management of CRBSI in patients with short- and long-term CVCs, in adults and children [6,20]. Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (LOE 2++ in adults). The choice of antibiotics must be based on patient risk factors, severity of infection and local resistance pattern and changed to a narrower-spectrum therapy once the infecting organism has been identified. The duration of systemic antimicrobial therapy after a CRBSI diagnosis depends on several factors including: catheter removal or retention, response to antimicrobial therapy within the first 48–72 h (resolution of fever and bacteremia), and the development of other complications (embolic tissue infection, septic thrombosis, or endocarditis) (LOE2++ in adults). There are no compelling data to support specific recommendations for the duration of therapy for device-related infection. The optimal duration of therapy for treating CRBSI in children with or without catheter removal has not been

established. Therefore, recommendations regarding the duration of therapy for pediatric patients with CRBSI mirror adult recommendations. In general, if the catheter is retained a 10–14-day course of systemic antimicrobial therapy is adequate, assuming a response to antimicrobial therapy within 48–72 h and no evidence of complications (defined as persistent bacteremia 72 h after appropriate treatment initiation, suppurative thrombophlebitis, endocarditis, osteomyelitis, or possible metastatic seeding) (LOE 2+).

Because of vascular access difficulties in children, it is often necessary to attempt CRBSI treatment without catheter removal. Several studies have reported successful CRBSI management among children without catheter removal [18] (LOE 2+) [22]; (LOE 3). In 52 children with SBS, of the 181 episodes in which the catheters were not promptly removed, renal insufficiency occurred in 12 (7%) cases, disseminated infection in 7 (4%), hypotension in 13 (7%), and mechanical ventilation in 10 (6%). Complications also occurred in 4 of the 14 episodes in which the catheter was promptly removed. Although there was no catheter management-dependent difference in time required to clear infection for Gram-positive and Gram-negative organisms, the time required to clear infection was significantly longer in episodes of infection caused by fungal organisms when the catheter was not removed promptly. Twelve patients died prior to hospital discharge, 5 from complications of their infections (n = 2 coagulase-positive staphylococci, n = 1 *Candida albicans*, n = 1 *Enterococcus faecalis*, n = 1 *Eschericia coli*). In all 5 of these patients, the catheter was not promptly removed [22].

Removal of the CVC is required if there is clinical deterioration or persisting or relapsing bacteremia, severe sepsis, suppurative thrombophlebitis, endocarditis or bloodstream infection that continues despite 72 h of antimicrobial therapy to which the infecting microbes are susceptible [6,20] (LOE 2++ in adults). Patients with a long-term CVC and an uncomplicated CRBSI with *Staphylococcus* aureus, *Pseudomonas* species or Candida require immediate removal of the infected CVC and a defined course of systemic antibiotic therapy, except in rare circumstances when no alternate venous access is available (LOE 2++ in adults). Treatment of catheter-associated fungemia without removal of the catheter has a low success rate and is associated with higher mortality (LOE 2++ in adults). Recent reports involving children with *Candida* CRBSI found that the addition of antifungal lock therapy led to a high cure rate without catheter removal, but there are insufficient data to recommend routine catheter salvage using this approach for this infection unless there are unusual extenuating circumstances [23,24] (LOE 3). Replacing catheters can be difficult in patients with limited access, and surgical complications can arise. As such, the risks of catheter retention in the setting of infection must be weighed against those of surgery and general anesthesia, as well as the consumption of the limited anatomical sites that are suited for catheter placement. Children treated for CRBSI without catheter removal should be closely monitored with clinical evaluation, additional blood cultures, and use of antibiotic lock therapy combined with systemic therapy for catheter salvage [6,20] (LOE 2+).

Uncomplicated exit site infections (i.e., those without systemic signs of infection, positive blood culture results, or purulence) may be managed with topical antimicrobial agents on the basis of the exit site culture results (LOE 2+). Catheter removal and systemic antibiotic therapy is recommended for patients with an apparent tunnel or port-site infection (LOE 2+) [6,20].

Antibiotic lock therapy has been recommended for the treatment of adults with CRBSI, always used in conjunction with systemic antibiotic therapy (LOE 2+). It involves installing a high concentration of an antibiotic to which the causative microbe is susceptible in the catheter lumen. Data on ethanol and antibiotic locks use as adjuncts to systemic antibiotic treatment in children with CRBSI is sparse and this therapy is not routinely recommended (LOE 3).

Contaminated PN and intravenous fluid have been reported to cause sepsis outbreaks. The contamination may have taken place during compounding of PN in the pharmacy or during handling of the solutions in the ward. Gram positive and –negative bacteria and Candida albicans were found to be the species most likely to contaminate PN during preparation or administration and have been implicated in more than 95% of all outbreaks and sporadic cases of nosocomial bloodstream infections related to contaminated parenteral admixtures [25–27] (LOE 3).

3.2. Mechanical complications

Mechanical events such as occlusion, leakage and dislodgement are commonly seen. The reported incidence of CVC mechanical complications in different series is 3.37 per 1000 days-catheter (95% CI: 2.76–4.12) [9] (LOE 3).

3.3. Occlusion

Catheter occlusions, in which blood cannot be drawn nor solutions infused, can occur from mechanical causes, precipitation of a medication or PN, or as the result of a thrombotic process. Recognition of the probable cause is critical to appropriate intervention and salvage of the catheter. Catheter occlusion can occur suddenly (usually caused by an intraluminal precipitate) or can develop over several days (usually clots).

3.3.1. Nonthrombotic occlusions

PN components (lipids or calcium–phosphorus complex) and, less frequently, incompatible drugs may precipitate and cause occlusion. Medication crystallization and precipitation within CVC usually occur when incompatible medications are administered. Adding a solution that returns the pH of the crystallized medication back into the normal range may dissolve the precipitate. When medications with a normally high pH (eg, phenytoin) crystallize in a central vascular device, sodium bicarbonate can be infused to raise the pH and the medication may revert to its liquid state. When low pH medications (eg, vancomycin) crystallize in a CVC, hydrochloric acid can be used to lower the pH and dissolve the precipitate occlusion [28,29] (LOE 3). Lipid occlusions may also occur and are more prevalent with silicone catheters because lipid emulsions adhere to silicone. Ethyl alcohol at a 70% solution may be used to dissolve lipid occlusions [30] (LOE 3).

Catheter kinking along the path of the CVC and tip positions against the vessel wall may create mechanical occlusions that prevent or reduce flow through catheter. Proper positioning of CVC catheters may prevent this complication which often occurs with shorter catheters with tips high in the superior vena cava [31] (LOE 3). Catheter “pinch-off” and “pinch-off syndrome” are terms used to describe the compression of a CVC between the clavicle and first rib. Over time, repeated compression (caused by shoulder and arm movement) can cause a mechanical obstruction, catheter injury with infusate leak or rupture. A contrast study or chest x-ray can be used to confirm or rule out catheter pinch-off [32] (LOE 3).

3.3.2. Thrombotic occlusion and CVC related thrombosis

R 14.7	**Thrombotic catheter occlusion and CVC related thrombosis require thorough investigation and treatment as they may be associated with significant morbidity (LOE 2–, RG B, strong recommendation, strong consensus)**

Thrombosis associated with a CVC can involve the catheter tip, the length of the catheter, or the catheterized vessel. The reported prevalence of CVC-related thrombosis in children varies, depending on the underlying diagnoses, diagnostic tests and index of suspicion/presence of symptoms. In the Canadian registry the incidence of CVC-related thrombosis in children with different diseases was 3.5 per 100,000 hospital admissions [33] (LOE 2++). In children receiving HPN, the incidence of CVC-related thrombosis was reported to range from 1 to 80%, with the lowest frequencies reflecting the clinical diagnosis of thrombosis and the highest frequencies reflecting venographic evidence of thrombosis [34] (LOE 2−).

The majority of CVC related thromboses are asymptomatic. Otherwise, the initial symptoms of line thrombosis in children receiving PN through CVC include mainly difficulty in flushing or obtaining blood from the catheter. Symptoms associated with superior vena cava (SVC) and inferior vena cava (IVC) occlusion also include head and neck swelling, pleural effusion, chemosis and plethora, and lower limb edema, respectively [35,36] (LOE 2−). Symptoms attributed to pulmonary emboli (PE) include dyspnea, stridor, hoarse cry and airway occlusion, and chest pain in older children [37] (LOE 2−).

A combination of ultrasound and venography imaging seem to be required for accurate diagnosis of CVC-related thrombosis in the upper venous system [38] (LOE 2+). Ultrasonography may be adequate for jugular thrombosis but inadequate for diagnosis of subclavian or SVC thrombosis. Nevertheless, one can start with this method, as it is non-invasive and easy to perform. If the result is negative and clinical suspicion is high, venography is the method of choice. In the future, magnetic resonance imaging may become a noninvasive alternative for invasive venography for the detection of CVC-related thrombosis [39] (LOE 2−).

Morbidity and mortality from thrombotic events are clinically significant and include loss of subsequent intravenous access, recurrent thrombosis, PE, postthrombotic syndrome and death.

The incidence of CVC-related thrombotic events in children receiving long-term PN varies from 1% based on clinical diagnosis to 35% based on ventilation perfusion scans or echocardiography to 75% based on venography [37,40–42]. (LOE 3). Specific thrombus-related mortality is however extremely low, with most studies of children receiving long-term PN reporting a mortality rate of 0% [40,41,43] (LOE 3).

3.3.2.1. Treatment of thrombotic catheter occlusion.

R 14.8 **Fibrinolytics are the drug class of choice used to treat thrombus-occluded catheters. Tissue plasminogen activator (tPA, alteplase) is currently the recommended agent; however, urokinase and recombinant urokinase (rUK) can also be used (LOE 2+, RG B, strong recommendation, strong consensus)**

Fibrinolytics are the drug class of choice used to treat thrombus-occluded catheters. Thrombolytic agents used to restore catheter patency are streptokinase, urokinase and tissue plasminogen activator (tPA). COOL (double blind placebo controlled, 149 patients) and COOL-2 (open label, 991 patients) (Cardiovascular Thrombolytic to Open Occluded Lines) have shown the role of alteplase, a recombinant fibrinolytic agent with a higher degree of fibrin selectivity, for restoration of patency of occluded venous catheters, without significant side effects [44,45] (LOE 2++). The populations in both trials consisted of adult and pediatric patients. Catheters' patency was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < .0001$ compared to placebo). Alteplase doses of 0.5–2 mg have been instilled into the CVC lumen with dwell times ranging from 30 to more than 240 min. Overall efficacy ranged from approximately 50%–90%, with greater efficacy generally reported with larger doses and longer dwell times. The Cathflo Activase Pediatric Study which was performed in 310 children reported a cumulative rate of restoration of catheter function after serial administration of a maximum of two doses of alteplase, each with a maximum dwell time of 120 min, of 82.9% (95% CI, 78.2–86.9%). No intracranial or other major bleeding or thrombo-embolic events occurred [46] (LOE 2++). Repeated doses of alteplase may be necessary if patency is not restored, as recommended by both the manufacturer and the American College of Chest Physicians ACCP) [43] (LOE 2++). Limitations of current studies of alteplase for catheter occlusion in children include small study populations and relative lack of pediatric-specific prospective trials.

The latest American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis, 9th ed states: “In pediatric patients, tPA is the agent of choice”. Reasons for this preference include a previous US Food and Drug Administration warning regarding urokinase, experimental evidence of improved clot lysis in vitro compared with urokinase and streptokinase, fibrin specificity, and low immunogenicity [47].

A recent review of thrombolytic treatment for catheter obstruction (studies in adults and children with different disorders and catheter types) reported that alteplase, one of the current therapies, clears 52% of obstructed catheters within 30 min with 86% overall clearance (after 2 doses, where necessary). Recombinant urokinase cleared 60% of catheters at 30 min but only 73% of catheters after repeated doses. Newer medications such as reteplase, tenecteplase and alfimeprase may have higher efficacy or shorter time to clearance. Reteplase is a new recombinant tissue plasminogen activator similar to alteplase but it lacks several structural domains. Therefore, penetration into the thrombus is improved, allowing fibrinolysis throughout the thrombus. Reteplase was instilled into 15 clotted catheters in children in a dose escalation trial. The dose of reteplase was started at 0.1 units and increased with increments of 0.1 units to a maximum dose of 0.4 units. Attempts to access the catheter were made every 15 min for 1 h. Twelve of the 15 catheters (80%) were patent after a mean dwell time of 38 min. No adverse events occurred. Reteplase seems to be as efficient and safe as alteplase, but may need shorter dwell times [48] (LOE 3). Recombinant urokinase may also have a role in prevention of thrombotic catheter occlusion [49] (LOE 2+).

3.3.2.2. Treatment of catheter-related thrombosis.

R 14.9 **The recommended management of acute and symptomatic CVC-related thrombosis depends on the requirement for the CVC and usually requires antithrombotic medication (LOE 2+, RG B, strong recommendation, strong consensus)**

In patients with catheter-related venous thrombosis, and a catheter *in situ*, anticoagulation, including low-molecular-weight heparin (LMWH) subcutaneously or unfractionated heparin (UFH) intravenously, is the main initial therapy. The aims of initial anticoagulant therapy are to prevent thrombus extension and subsequent pulmonary embolization. After 3 months of full anticoagulant therapy, switching to prophylactic doses of anticoagulation therapy is recommended and this should be administered until the removal of the CVC [43] (LOE 2+).

Thrombolytic therapy is usually not recommended unless a major vessel occlusion is involved causing critical compromise of organs or limbs (LOE 2+). Thrombolytics stimulate thrombus resolution more rapidly than heparin anticoagulation, particularly if the clot is relatively acute, roughly less than 2 weeks old. However, this benefit must be weighed against the risk of major bleeding, which is greater than with anticoagulation alone. If thrombolysis is required, tPA is used rather than other lytic agents [49–52] (LOE

2+). Compared to urokinase and streptokinase, tPA has shown improved clot lysis in vitro, fibrin specificity and low immunogenicity [53,54] (LOE 3). The success rate of thrombolysis in pediatric patients varies. Reported rate of complete thrombus resolution is 53%, 43%, and 69%, respectively when using streptokinase, urokinase, or tPA [54,55] (LOE 3). The major drawback of thrombolytic therapy is the increased number of major bleeding complications. In retrospective case series these complications occurred in 0%–40% of the children treated with alteplase [50] (LOE 4). Alternatively, a successful combination of chemical thrombolysis and balloon angioplasty or endovascular recanalization for catheter salvage has been described in the literature [56,57] (LOE 5).

The recommended management of radiographically detected asymptomatic CVC-related thrombosis is less clear and based mainly on expert opinion and less on evidence-based data. Since asymptomatic CVC-related thrombosis is believed to have clinical significance in children, treatment with anticoagulation is recommended in the absence of contraindications [43] (LOE 2+). For children receiving long-term HPN thromboprophylaxis with vitamin K antagonists (VKAs) has been suggested [43] (LOE 2+).

A recent Cochrane systematic review which assessed the efficacy and safety of different interventions used to restore patency of occluded CVC lumens in adults and children, identified only 7 (2 in children) randomized or quasi-randomized controlled trials (RCTs) [58]. None of the included studies investigated chemical or surgical interventions for treating occluded CVCs. All 7 studies investigated different comparisons or strengths of thrombolytic or anticoagulant therapies for treating CVC occlusion caused by a thrombus. There was some evidence from 2 studies that investigated urokinase vs. placebo (RR 2.09, 95% CI 1.47 to 2.95) and alteplase 2 mg/2 ml vs placebo (2 studies, RR 4.19, 95% CI 2.44 to 7.20) that these two drug interventions may be effective in treating occlusion of CVC lumens caused by thrombosis [59,60] (LOE 2+).

3.4. Extravasation, breakage and migration

R 14.10	**Proper positioning of the catheter tip and immediate investigation when catheter breakage or fluid extravasation are suspected should be implemented in order to prevent the occurrence of significant morbidity (LOE 4, RG 0, strong recommendation, strong consensus)**
R 14.11	**Appropriate measures to secure the catheter in place and education for users about correct maintenance and safety of the catheter are strongly recommended (GPP, strong recommendation, strong consensus)**

Extravasation, the leakage of infusate from a vein into the subcutaneous space, is a relatively infrequent complication of central venous catheters. Life-threatening extravasation complications have occasionally been reported including pleural or pericardial effusion and cardiac tamponade [61,62]. Rarely reported sites of extravasation include the pulmonary parenchyma [63,64], renal pelvis [65], scrotum [66,67], retroperitoneal space [68], spinal epidural space [69] and subdural space [70] and even into pharynx causing oral aspiration of PN infusate [71] (LOE 4). Massive PN fluid extravasation into subcutaneous tissue has been treated with recombinant human hyaluronidase (rHuPH20) [72] (LOE 5). Approved by the United States Food and Drug Administration (FDA) as an adjuvant to increase the absorption and dispersion of other injected drugs in adults and children, rHuPH20 (Hylenex [Baxter International Inc., Deerfield, IL]) has been reported to be safe and well tolerated when used to facilitate the absorption of hydration fluids and subcutaneous drugs [73].

Catheters that loop at acute angles are at risk for fracture. The most common signs of a fractured catheter are local swelling, pain, or skin site leakage on injection. Other less common signs are resistance on injection, inability to withdraw, cough, and chest pain. In cases of suspected catheter fracture, it may be prudent to obtain radiographic studies encompassing the upper extremities and chest, even in the asymptomatic patient. The catheter tip can migrate to locations such as the internal jugular vein in the neck or contralateral brachiocephalic vein. Intravascular and intracardiac embolization of the catheter fragments is a severe and rare complication and accounts for <1% of all reported complications [74] (LOE 4). Giving the high mortality and the wide range of complications that may result, it is important to remove the catheter fragment immediately unless contraindicated. Percutaneous and open surgery are both options for the retrieval of catheter fragments. Retrieval of fragmented catheter emboli can now be safely and effectively accomplished percutaneously [75] (LOE 5).

Inadvertent device damage can occur during routine care and maintenance. Damage to tunneled catheters and PICCs is generally repaired by using a specially designed repair kit. Vascular erosion is a rare but life-threatening CVC complication. Improvements in catheter material properties have greatly decreased the incidence of vascular erosion. Any central vascular device catheter with its tip adjoining the vessel wall at a near perpendicular angle should be monitored closely, or preferably repositioned [76] (LOE 4).

3.5. Loss of vascular access

Careful management of vascular access in children with IF will allow for long-term access and prevent the development of access difficulties that can limit the ability to provide PN and lead to intestinal or multi-organ transplant. Finally, in patients that do develop significant thrombosis or occlusion of all of their central vessels, innovative methods of obtaining central venous access have been described, including transhepatic catheters, translumbar or percutaneous mammary catheters, and gonadal vein catheters [77] (LOE 4). Interventional radiology assistance is often helpful in these complex patients. Using these general guidelines, loss of central venous access should be an extremely rare indication for intestinal transplantation. Overall, 10% of IF patients referred for a small bowel transplant assessment had difficulty with placement of a central venous catheter for PN [78] (LOE 3).

4. Complications and considerations related to the composition of the PN solution

4.1. Stability

R 14.12	**PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution (GPP, strong recommendation, strong consensus)**
R 14.13	**A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives (GPP, strong recommendation, strong consensus)**
R 14.14	**Alternative ingredients should not be substituted without expert advice or repeat validation (GPP, strong recommendation, strong consensus)**
R 14.15	**Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation (GPP, strong recommendation, strong consensus)**
R 14.16	**If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to (GPP, strong recommendation, strong consensus)**
R 14.17	**When '2 in 1' admixtures with Y-site lipids added are used, addition of lipids should be fully validated by the manufacturer or accredited laboratory or the lipid infused through an alternative line (GPP, strong recommendation, strong consensus)**

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 [79] (LOE 4). There may be variability through factors such as the variation in pH between different batches of glucose due to decomposition during autoclaving [79,80] (LOE 4) and changes in trace element profiles due to adsorption onto, or leaching from, admixture containers and tubing [81–83] (LOE 3).

A '3 in 1' admixture is administered through a single line and the emulsion stability has been confirmed for the formulation [79,84–86]. 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 [87–89] (LOE 3). As there are risks associated with instability of regimens, it has been recommended that PN admixtures be administered through a terminal filter [90] (LOE 3).

The use of organic-bound phosphates reduces the risk of calcium-phosphate precipitation and hence potential clinical risks [91]. Addition of heparin to admixtures, even where validated, carries a small risk of emulsion instability occurring with individual batches of heparin [92,93] (LOE 4).

4.2. Drug compatibility

R 14.18	**Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory (GPP, strong recommendation, strong consensus)**

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 [87] (LOE 3). 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 [94,95] (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 [79] (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 [96] (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 [96] (LOE 4). This means that any study of drug compatibility with PN can only be reliably applied to the particular product 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 [97,98] (LOE 3).

4.3. Peroxidation, light protection and vitamin stability

R 14.19	**Multi-layer bags which are impermeable to oxygen are recommended for PN administration (GPP, strong recommendation, strong consensus)**
R 14.20	**Light protection is recommended for both PN bags and administration sets (LOE 3, RG 0, strong recommendation, strong consensus)**

The use of PUFAs in PN increases the risk of peroxidation and is one of the potential factors in the development of IFALD. The contributing factors to peroxidation of lipid emulsions are exposure to oxygen within the bag, photo-degradation, and an increasing ambient temperature, the type of container used, trace elements in the formulation and the content of alpha-tocopherol within the bag [84,99]. Peroxidation can therefore be minimised by the use of multi-layer bags, which reduce the amount of oxygen in the bag, a formulation with sufficient amounts of anti-oxidant alpha-tocopherol, which acts as free radical scavenger and anti-oxidant ascorbic acid [83,100] (LOE 3).

Vitamins are prone to stability issues due to photo-degradation, oxidation and interactions with PN bags and administration sets [100]. Ascorbic acid is very susceptible to oxidation. This is important with respect to the formation of oxalic acid, a by-product of oxidation which can form calcium oxalate crystals with calcium salts in the formulation. Oxidation of ascorbic acid can be reduced by the use of multi-layer bags. The vitamins which are particularly susceptible to photo-degradation are retinol and riboflavin. The photo-degradation can be quite significant with a potential clinical impact to the patient. This effect is seen when the bags are exposed to daylight but also artificial ambient light on the ward. Lipid opacity is not sufficient to prevent photo-degradation therefore the bags and administration sets both need to be light protective [100] (LOE 3).

4.4. Osmolarity

RG 14.21	**The recommended delivery site for PN is via a central line; however peripheral PN can also be given for short periods (LOE 3; RG 0, strong recommendation, strong consensus)**
RG 14.22	**The osmolarity of peripheral PN solution should be kept less than 900 mosmol/l (LOE 3, RG 0, conditional recommendation, strong consensus)**

Parenteral nutrition should be infused via a central venous line to minimise the risks of thrombophlebitis and extravasation [101] (LOE 3). PN solutions are inherently acidic due to the glucose and amino acid solutions used but the osmolar load from the electrolytes also needs to be taken into account during the formulation

process. Lipid emulsions are isotonic and are therefore suitable for either peripheral or central use. Two recent retrospective studies have reported contradictory results with regard to adverse events of peripheral infused PN infusions with >1000 mOsm/l [105] or >900 mOsm [102] in neonates and older children. Dugan S reported increase rate of thromboflebitis events and infiltration in both neonates and older children given PPN with osmolarity >1000 mOsm/l [103]. By contrast, Cies et all found similar rates of adverse events in both neonates and children given either less or more than 900 mOsm/L PN solutions into peripheral sites [104]. In adults ASPEN recommends a less than 900 mOsm/l for PN solutions infused peripherally [104].

When peripheral PN is infused, solution' osmolarity of less than 900 mosmol/l reduces the risk of thromboflebitis [102–104] (LOE 3).

5. Metabolic complications of PN

5.1. Metabolic bone disease

R 14.23	**In children on home PN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed (LOE 2+, RG B, strong recommendation, strong consensus)**
R 14.24	**Ingredients with the lowest amount of aluminum are advocated for the preparation of parenteral nutrition solutions provided to patients receiving PN (LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.25	**Regular assessment of bone mineralization should be performed (LOE 2−, RG B, strong recommendation, strong consensus)**

PN-related metabolic bone disease (MBD) with symptoms and signs of decrease in bone mineral density (BMD), osteoporosis, pain and fractures was reported not only in adults but in children on long-term parenteral nutrition as well [105–107] (LOE 2+). In children, increased risk of MBD was reported both during and after weaning from long-term PN [108–111] (LOE 2+). The cause of MBD is most probably multifactorial, including mechanisms related to both the underlying disease and PN: excess of vitamin D, phosphorus, nitrogen and amino acids intake as well as energy imbalance and aluminium contamination [112] (LOE 2−).

Pediatric patients receiving long-term PN are at risk for aluminium toxicity and consequential MBD even at present [113,114] (LOE 2++). Neonates who are exposed to parenteral aluminum intake may have reduced lumbar spine and hip bone mass during adolescence, which may predispose to osteoporosis and hip fracture later in life [115] (LOE 1−). Use of aluminium contaminated products should be kept to a minimum (e.g. by avoiding glass vials and certain mineral and trace element sources known to have high aluminium content). In order to practically achieve this goal, ingredients with measured and labelled aluminium content should be preferred for the preparation of pediatric PN solutions.

Regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed as part of the evaluation of MBD in patients on PN. Elevated serum alkaline phosphatase activity in infants on PN indicates bone rather than hepatic origin [116] (LOE 3). Diagnosis of bone disease relies primarily on the measurement of bone mineralization using validated imaging methods (e.g. dual energy X-ray absorptiometry). The International Society for Clinical Densitometry recommends a minimum interval of 6–12 months between DXA scans, depending on clinical presentation, taking into account the previous z-score results as well as previous occurrence of fractures [117].

Bone turnover markers (osteocalcin, c-telopeptide) may be useful indicators for identifying children on long-term PN at risk of MBD [118] (LOE 2−).

Very premature newborns have an increased risk of low bone mass and metabolic bone disease. Short-term decline in bone strength may be prevented by higher calcium and phosphorus intake via PN [119] (LOE 1−) or by early initiation of PN [120] (LOE 2+).

Bisphosphonate treatment was described to improve BMD in adults on PN; in infants, published experience of bisphosphonate use is very limited [121,122] (LOE 4).

5.2. Hepatobiliary complications of parenteral nutrition

R 14.26	**The risk of liver disease can be decreased by reducing patient-related and PN-related risk factors (LOE 2+, RG B, strong recommendation, strong consensus)**
R 14.27	**In patients with intestinal failure-associated liver disease, maximizing enteral intake as tolerated EN may improve liver disease outcome (GPP, strong recommendation, strong consensus)**
R 14.28	**In patients on long-term and home PN, cycling of PN infusion is recommended as soon as metabolic and fluid status allows (LOE 3, RG 0, strong recommendation, strong consensus)**
R 14.29	**Pure soybean-based lipid emulsions should be avoided in the presence of cholestasis (LOE 3, RG 0, strong recommendation, strong consensus)**
R 14.30	**The use of mixed LEs may be encouraged in IF patients for long term PN (LOE 3, RG 0, conditional recommendation, strong consensus)**
R 14.31	**The initiation of ursodeoxycholic acid may be considered in the presence of biochemical signs of cholestasis (LOE 3, RG 0, conditional recommendation, strong consensus)**
R 14.32	**Early referral to an experienced pediatric intestinal failure rehabilitation/transplantation centre is recommended in infants/children with intestinal failure-associated liver disease (GPP, strong recommendation, strong consensus)**

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 [4,123] (LOE 2+). It probably results from the interaction of many factors related to the underlying disease, infectious episodes, surgery and components of the PN solution [4,123] (LOE 2+).

5.2.1. Patient and/or disease related factors

Children requiring long-term PN are at high risk of developing liver disease. Absence of oral feeding impairs bile flow and increases the risk of biliary sludge formation. Intestinal failure, especially intestinal atresia and gastrochisis, may be associated with disruption of bile acid enterohepatic circulation due to ileal resection, bacterial overgrowth due to bowel obstruction. These, as well as severe motility disorders and ileocaecal valve resection, are all factors thought to contribute to PN-associated liver diseases

[123,124] (LOE 2+) [125]; (LOE 2−). 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 sepsis occur [4,126] (LOE 2+).

5.2.2. PN related factors

PN may have additional deleterious effects on the liver:

- It has been demonstrated that an excess of total energy delivered induces liver lesions, which are reversible when the energy supply is decreased [124] (LOE 2+) [127]; (LOE 2−).
- Excessive or inadequate amino acid supply [4,123] (LOE 2+) [128]; (LOE 2−).
- Continuous PN infusion and/or excessive glucose intake is associated with hyperinsulinism and subsequent steatosis [4,129] (LOE 2+) [130]; (LOE 2−), although it is not clear whether this is also associated with cholestatic liver disease.
- The role of excessive fat supply and subsequent lipoperoxidation has been suggested to contribute to PNALD [128,131,132] (LOE 2−). Phytosterols contained in lipid emulsions may contribute to liver dysfunction [133,134] (LOE 2−). The role of various lipid emulsions in the development and treatment of liver disease is detailed in the Lipid chapter.

5.2.3. Monitoring

Regular monitoring of hepatic function is extremely important during PN in order to minimize or correct factors responsible for liver disease. Elevation of plasma alkaline phosphatase and gamma-glutamyl transferase activities appears earlier than hyperbilirubinemia, but these are not specific laboratory markers. 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.

Liver and intestinal transplant 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) [135] (LOE 2−).

5.2.4. Prevention and treatment of cholestasis

Some measures may limit or reverse liver disease including:

- Early referral to an experienced paediatric intestinal rehabilitation centre [136] (LOE 3).
- The stimulation of the entero-biliary axis by promoting oral or enteral feeding with breast milk or long-chain triglycerides containing formulae, even minimal feeding [123,124] (LOE 2+) [137], (LOE 2−).
- The reduction of intraluminal bacterial overgrowth caused by intestinal stasis by giving metronidazole or gentamicin [4,123] and/or by performing venting enterostomy or tapering enteroplasty [138] (LOE 2−) have been evaluated in few studies but no recommendations can be made based on these studies.
- The evidence for the use of ursodeoxycholic acid (UDCA) is limited to two randomized controlled studies for prevention of cholestasis and few other observational/retrospective studies that investigated UDCA as a therapeutic agent for the treatment of cholestasis. The studies included a heterogenous population of subjects. The prevention studies suggest that UDCA may be effective at reducing biochemical signs of liver cholestasis without significant infant intolerance to the treatment. No data on liver histology or liver disease outcomes are available [134,139] (LOE 2−) [140]; (LOE 3).
- Cyclic PN for most infants and children exception of very low birth weight infants [4,129] (LOE 2+).
- Reduction of total calorie intake and reduction of lipid dosage from PN [141] (LOE 1−) [142]; (LOE 2+).
- Fish-oil containing or based lipids may reverse PNALD [4,143] (LOE 2+) [144–147]; (LOE 2−) [148]; (LOE 3).

6. Growth retardation

R 14.33	**Pediatric patients on long term PN require regular monitoring of growth and body composition (LOE 2−, RG B, strong recommendation, strong consensus)**

A child dependent on PN must receive adequate nutrition not only to meet basic metabolic requirements but also to allow normal growth [149] (LOE 1).

Studies in children on long-term parenteral nutrition have reported high prevalence of growth deficits and abnormal body composition. Pichler et al. identified short stature (-2SD height for age) in half of their patients with short bowel and in 70% of children with different enteropathies [107]. Body composition abnormalities, including high/low body mass index and altered lean and fat mass were described in a group of children and adolescents aged 5–20 years [150]. Since abnormalities in body composition may have long-term metabolic consequences, growth and body composition monitoring are important parameters to investigate and monitor in these children.

Conflict of interest

None declared.

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