

Complications of Long-Term Home Total Parenteral Nutrition

Their Identification, Prevention and Treatment

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The purpose of this review is to describe the most common complications of home total parenteral nutrition, their identification, treatment and prevention. Data sources were manuscripts and abstracts published in the English literature since 1968. Studies were selected for summarization in this review on the basis of clinical relevance to the practicing clinician. Home total parenteral nutrition is a relatively safe, life-saving method for nutrient delivery in patients with compromised gastrointestinal function. However, numerous complications, with associated morbidity and mortality, involving the delivery system and the gastrointestinal, renal, and skeletal systems may develop. Catheter-related complications are often preventable and treatable when they occur, although renal and bone abnormalities have elusive etiologies.

KEY WORDS: parenteral nutrition; catheter infection; catheter occlusion; catheter care; intestine; intestinal permeability; nonalcoholic steatohepatitis; metabolic bone disease.

The first patient was sent home to receive parenteral nutrition in 1968 (1). Since then, the number of patients that require this therapy has grown to approximately 40,000 yearly as recently as 1992 (the most recent statistics available) (2). While many of these patients need TPN (total parenteral nutrition) temporarily because of such illnesses as high-dose chemotherapy, bone marrow transplant, hyperemesis gravidarum, etc, some patients with short bowel syndrome, radiation enteritis, malabsorption, or chronic intestinal pseudoobstruction may require TPN on a permanent basis. Internists are often called upon to manage these patients and should be aware of the complications of home TPN, how to prevent them if possible, and how to manage them when they do occur. This review is intended for the practitioner,

although areas where additional research is necessary are highlighted. The objective is to inform the practitioner who manages patients that receive home TPN of the possible complications of this therapy and methods that may be employed to treat and prevent them. I have confined the review to the adult human experience, with pediatric or animal data presented only to substantiate similar observations in adult humans. Patient survival, as well as specific catheter-related (infectious, catheter occlusion), renal, gastrointestinal, hepatobiliary, and skeletal complications are discussed together with the existing data on diagnosis and monitoring, pathogenesis, prevention and treatment of each.

METHODS

A Medline search was conducted for the years 1968–1999 for parenteral nutrition, cross-referenced with complications and the specific complications of infection, sepsis, catheter, thrombosis, superior vena cava syndrome, kidney, liver, hepatic steatosis, steato-

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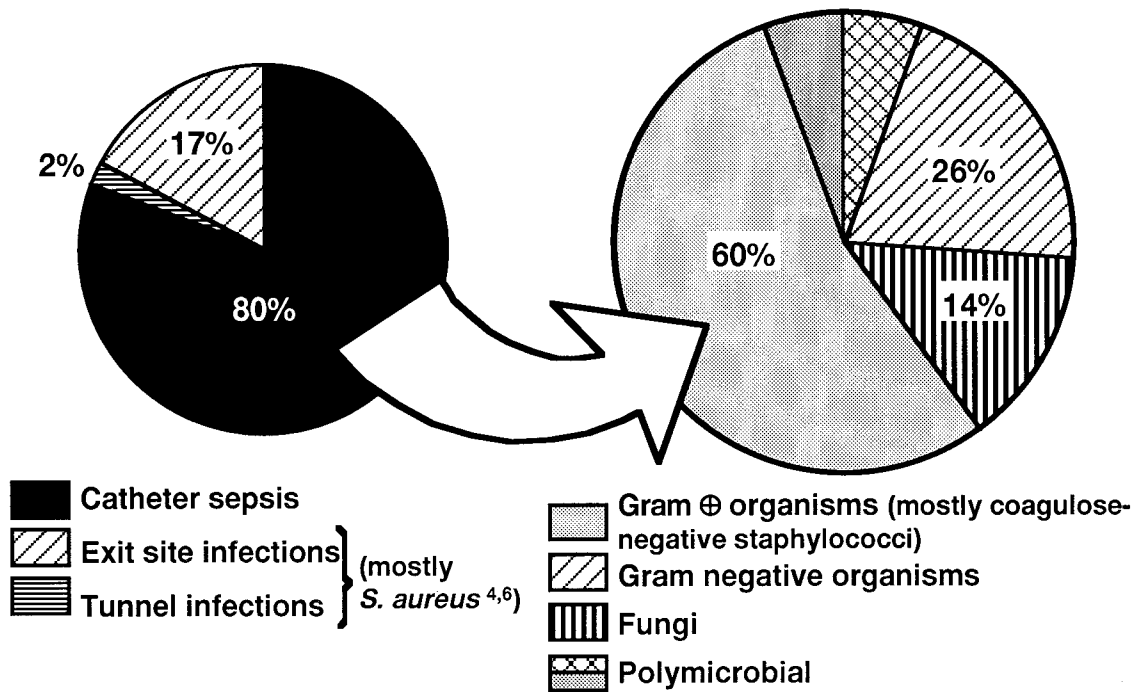


Fig 1. The Incidence of catheter-related infections during TPN.

hepatitis, cholestasis, bone, osteoporosis, osteomalacia, gastroparesis, small intestine, gallstones, and cholecystitis. The authors's extensive file collection of published articles and abstracts was also extensively utilized.

SURVIVAL

The vast majority of patients that require home TPN die from their underlying disease rather than from TPN-related complications (2, 3). Survival rates are ≥87% at one year for patients with benign gastrointestinal disorders (91% at one year, 70% at three years, and 62% at five years) (3), although for patients with other disorders the survival is 10–50% at one years (2). Survival figures are >90% for younger patients with Crohn's disease. Rehospitalizations and therapy-related complications accounted for 5% of deaths in the USA [11% in France (3)] (2). Therapy-related complications occurred approximately once yearly except for patients with AIDS, cancer, and hyperemesis gravidarum, where the incidence was three or four times yearly (2). Death rate is unrelated to residual bowel, but is associated with the presence of intestinal stasis, including obstruction and pseudoobstruction (3). Several potentially serious complications may be encountered that may have significant impact on patient survival and morbidity.

CATHETER-RELATED COMPLICATIONS

Catheter-Related Infections

The most commonly encountered catheter-related complication is infection. There are three types of catheter-related infections (Figure 1): catheter sepsis, the most common (4); exit site or cuff infections (erythema or purulence at the catheter skin exit site related to an infected subcutaneous cuff which anchors the catheter); and tunnel infections (erythema and tenderness over the subcutaneous catheter tract), the least common.

Catheter Sepsis. A high index of suspicion is often required in order to diagnose catheter sepsis in its earliest state where it may manifest initially only by fever or shortness of breath only during TPN infusion, prior to the development of rigors, hypotension, and other manifestations of frank sepsis. It is important for the patient to be trained that these symptoms should prompt an immediate call to their physician. The algorithm in Figure 2 addresses diagnosis and treatment. All patients in whom catheter sepsis is suspected should have blood cultures obtained from the catheter and peripherally, their peripheral blood smear examined for the presence of budding yeast (5), and blood fungal cultures obtained. It is important that sufficient blood be obtained for culture

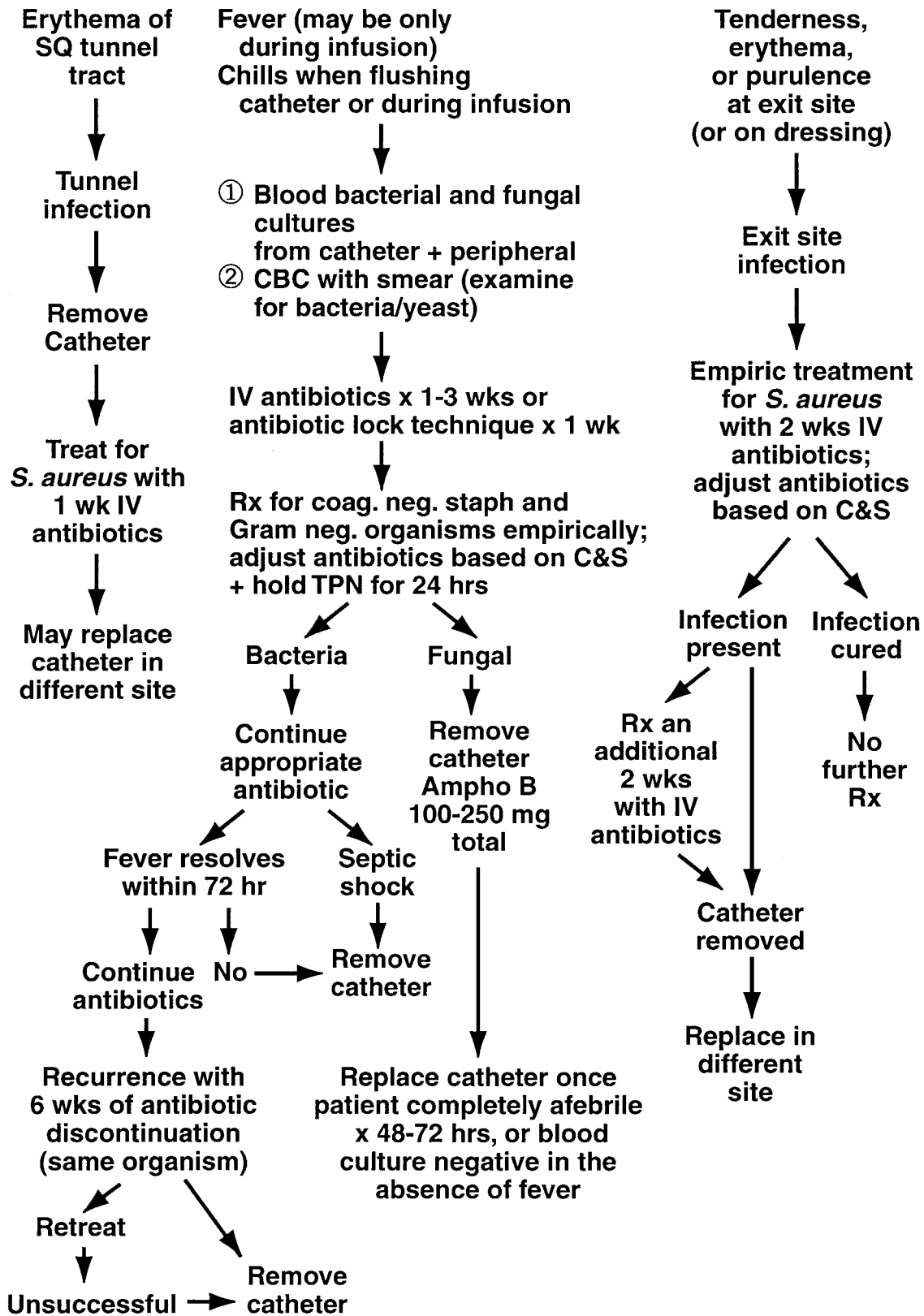


Fig 2. Suggested algorithm for the diagnosis and treatment of catheter-related infections.

TABLE 1. COMPLICATIONS OF LONG-TERM TPN

| |
|--|
| Infections |
| (0.4/yr; 0.5/yr in children) (4) |
| Catheter sepsis |
| Exit site infection |
| Tunnel infection |
| Catheter occlusion |
| Thrombosis (0.07/yr) (55, 76a-76d) |
| Mineral or lipid precipitate (79-86) |
| Renal (87-91) |
| Decreased GFR |
| Tubular dysfunction |
| Gastrointestinal |
| Gastroparesis (95-97) |
| Intestinal hypoplasia (?) (98-102) |
| Metabolic bone disease (107-135) |
| Osteomalacia |
| Osteoporosis |
| Hepatic disease (15-40% after 3 yr) (136-138) |
| Hepatic steatosis (145,159-164) |
| Cholestasis (139-142,146-148,166) |
| Phospholipidosis (175) |
| Biliary Disease (up to 100% after 6 weeks) (183-191) |
| Biliary sludge |
| Gallstones |

(10-20 ml) (6). Although it may be a good idea to keep a sample from the patient's most recent TPN bag in case an unusual organism is cultured from their blood, this should not be done routinely because of the expense and the extreme rarity of contaminated TPN in the United States. We generally initiate treatment in the hospital, with patients discharged home to complete their antimicrobial course when stable. If the patient lives close to a medical facility and is otherwise stable, cultures can be obtained by home nurses and empiric antibiotics initiated at home.

A single bacterial count of >100 CFU/ml from the catheter or a colony count ratio of 4:1 (central versus peripheral blood) is a reliable identifier of catheter sepsis (7, 8), although the diagnosis must often be made on a clinical basis when other potential infection sources have been excluded, especially if blood cannot be obtained from the catheter and one is considering an attempt at catheter salvage. Many different organisms may cause catheter infections (Table 2). Most are gram-positive bacteria, although infections with gram negative bacteria or fungi are frequent. (Figure 1).

Treatment of Catheter Sepsis. We hold TPN for 24 hr (longer if the patient is unstable) in order to effect catheter sterilization and to prevent further bloodstream seeding. Aggressive initial antimicrobial therapy with broad-spectrum antibiotics such as vancomycin and gentamicin may be useful in keeping the mortality rate low (4). Therapy can be adjusted once blood culture results are available (4, 9-12). It is important to choose antimicrobial therapy for the home patient that can be administered once or twice daily (eg, before and after the TPN infusion) in order to avoid excessive catheter manipulations, which are inconvenient and potentially invite the risk of yet another infection.. Antibiotics should be selected that are compatible with TPN, although vigorous catheter flushing can be done before and after the antibiotics are infused. It has been recommended to continue antibiotic treatment for four weeks, although the supporting data are largely anecdota (4). Others have

TABLE 2. ORGANISMS CAUSING INFECTIONS IN HOME TOTAL PARENTERAL NUTRITION PATIENTS*

| <i>Gram positive</i> | <i>Gram negative</i> | <i>Fungi</i> | <i>Mycobacteria</i> |
|----------------------------------|--------------------------------------|------------------------------|---------------------|
| <i>Bacillus</i> species | <i>Acinetobacter antiitritus</i> | <i>Candida albicans</i> | <i>M. avium</i> |
| <i>Corynebacterium</i> | <i>Acinetobacter diversus</i> | <i>Candida glabrata</i> | <i>M. chelonae</i> |
| <i>Enterococcus durans</i> | <i>Acinetobacter twofill</i> | <i>Candida guilliemondii</i> | <i>M. fortuitum</i> |
| <i>Enterococcus faecalis</i> | CDC group VE-2 | <i>Candida parapsilosis</i> | <i>M. xenopi</i> |
| <i>Moraxella osloensis</i> | <i>Citrobacter diversus</i> | <i>Candida tropicalis</i> | <i>M. smematis</i> |
| <i>Peptostreptococcus</i> | <i>Citrobacter freundii</i> | <i>Mallessezia furfur</i> | |
| <i>Propionibacterium</i> | <i>Enterobacter agglomerans</i> spp. | <i>Rhodotorula pilimanae</i> | |
| <i>Staphylococcus aureus</i> | <i>Enterobacter cloacae</i> | <i>Hansenula</i> spp. | |
| Coagulase-negative staphylococci | <i>Escherichia coli</i> | | |
| <i>Staphylococcus hominis</i> | <i>Klebsiella oxytoca</i> | | |
| <i>Streptococcus faecalis</i> | <i>Klebsiella pneumoniae</i> | | |
| Group B streptococci | <i>Klyuvera</i> spp. | | |
| <i>Streptococcus mitis</i> | <i>Lactobacillus</i> | | |
| <i>Streptococcus viridans</i> | <i>Oerskovia</i> spp. | | |
| | <i>Pseudomonas seruginosa</i> | | |
| | <i>Pseudomonas capacia</i> | | |
| | <i>Pseudomonas pickettii</i> | | |

*Adapted from Buchman et al. JPEN 18:299, 1994 (with permission)

used a median of seven days of intravenous antibiotic therapy and reported <10% recurrence (13).

A newer method of antibiotic delivery, the antibiotic lock technique, whereby a highly concentrated antibiotic solution is instilled into the catheter in a volume sufficient only to fill the catheter, twice daily (eg, before and after TPN infusion) for one to two weeks has been described (14–16). Reported success rates have been >90%, although treatment of fungal infections in this fashion has been unsuccessful (15). Amikacin (1.5 mg/ml), gentamicin (5 mg/ml), minocycline (0.2 mg/ml), and vancomycin (1.0–5.0 mg/ml) have been used. This technique is much less expensive than systemic antibiotics, appears to be more successful, and is more convenient for the patient.

A major issue in the treatment of TPN-related infections is catheter removal (Figure 2). Most episodes of catheter sepsis can be treated successfully without catheter removal (4, 9–11, 17). The catheter should be removed with fungal infections (4, 10, 11, 18), septic shock, or failure to defervesce and otherwise improve within 48–72 hr from the start of antibiotic therapy. Delayed catheter removal infected by fungi is associated with increased mortality (18, 19). Catheter replacement may occur once the patient has been completely afebrile for 48–72 hr. Catheter removal should be followed by a week of appropriate intravenous antibiotics, although there are few data on optimal treatment duration. Fungal infections generally require 100–250 mg of amphotericin B in addition to catheter removal (4). There has been little experience with fluconazole and other antifungals in this setting (20).

Prevention of Catheter Sepsis. The infection risk appears similar with either tunneled (Hickman/Broviac/Groshong type) external catheters versus the implanted reservoir catheter (21, 22). However, the risk of infection is significantly greater with triple-lumen and with nontunneled catheters (other than PICC) (23–26). The tunneling technique employs a tunnel created in the subcutaneous tissue which the catheter traverses on its way out to the skin. This allows for a longer, and more indirect route for bacteria that may enter the vein from the skin exit site. The infection risk may be greater when a needleless system is used (27), although that probably relates to a hub design that permits infusion solution to remain in the injection cap where it may become contaminated. Infection rates are probably greater in children because of a child's inability to effect good catheter care and greater chance for contamination of the exit site (4). Infection rates are also significantly greater in

patients with AIDS, possibly related to their immunocompromised state, although the same has not been found with recent chemotherapy or bone marrow transplant patients who used a similar catheter care protocol to that of patients with AIDS (4, 28). There is no data on the risk of central venous catheter infection in patients with AIDS in the era of antiretroviral therapy. Prophylactic antibiotic infusion prior to invasive procedures on the basis of an indwelling catheter does not prevent subsequent catheter infection (29).

Catheter Care. Catheter care technique is arguably the most important determinant of the incidence of catheter infection (4, 26, 29). The primary sources for infections are the skin at the catheter exit site (30) and the catheter hub (31–33). There is no substitution for proper cleaning of these sites. Evidence suggests that the nurse or patient's hand may contaminate both the exit site and catheter hub during catheter manipulations such as connecting or disconnecting TPN (34). For virulent organisms such as *Pseudomonas aeruginosa*, even a single inoculum may be sufficient to result in catheter sepsis (35). Hub contamination at the junction between the catheter and infusion line may be the initial process involved in endoluminal bacterial seeding (36). Luer locks have no antibacterial properties and require strict aseptic manipulation. Improvement in catheter hub care results in significantly decreased infection risk (33). This includes avoidance of three-way stopcocks because of the risk of hub contamination (37, 38). Accepted methods of catheter and hub care are described in Table 3.

Exit Site and Tunnel Infections. Most exit site and tunnel infections are caused by organisms present on the skin, especially *Staphylococcus* species (4). Purulent drainage should be cultured and initial therapy provided with vancomycin (4, 39). Neither exit site tunnel infections are systemic infections, and they are rarely associated with fever or leukocytosis. However, delayed treatment may lead to more serious sequelae. Two weeks of therapy has been recommended, although the data are largely anecdota (4). Most exit site infections can be treated successfully without catheter removal (4, 9–11, 17). Antibiotic penetration of the subcutaneous tunnel is suboptimal. Therefore, catheter removal is required for tunnel infections.

Prevention of Exit Site and Tunnel Infections. As with the prevention of catheter sepsis, exit site care is the most reliable determinant of infection risk. Appropriate dressing changes and care of the exit site are described in Table 3. Newly designed hubs and

TABLE 3. CATHETER CARE

| <i>Catheter and Hub</i> | <i>Dressing</i> |
|---|---|
| 3–6 applications of 70% isopropyl alcohol followed by 3–6 applications of 1% povidone-iodine (4, 38a); allow povidone-iodine to dry; may substitute 2% chlorhexidine when available or 1 application of H ₂ O ₂ followed by 2 applications of either 0.5% iodine tincture or 0.05% chlorhexidine (40a, 41a) | Iodophor ointment at catheter exit site? (38a) Prepare site with 3–6 applications of 70% isopropyl alcohol followed by 3–6 applications of 1% povidone-iodine (4, 39a); allow povidone-iodine to dry 1 application of 2% chlorhexidine (41a) Gauze dressing (may be covered by transparent polyurethane film dressing changed 2×/wk or when wet) |

connection devices, not currently available in the United States, have been associated with a lower incidence of infection (40–42), although an antibiotic-impregnated catheter cuff was not (43). Regardless of how good the equipment or the technique, catheter-related infection is most easily avoided if the catheter is not used for anything other than TPN. Therefore, it is my practice to never use a central line (especially a home TPN catheter) for temporary medical delivery (except for treatment of a catheter-related infection) if peripheral access is available. In the rare absence of a peripheral vein, the catheter must be prepared appropriately *each* time, prior to medication injection.

Catheter Dressings and Dressing Changes. Less frequent dressing changes, and the use of gauze rather than transparent polyurethane dressings have been associated with a lower risk for catheter infection (44–49). Increased bacterial colonization was noted under the transparent dressings. This may result in part from moisture accumulation under such dressings. These data are from inpatient populations. There have been no studies of which I am aware on the optimal frequency of dressing changes in home TPN patients with tunneled or PIC catheters or that compare gauze to transparent dressings in HTPN patients. Whether the results from inpatient studies, regardless of their shortcomings, can be generalized to this patient group, is unclear.

Catheter Occlusions

Occlusions are the second most common catheter-related problem. They occur either because of thrombus, precipitate formation, or mechanical problems related to the catheter. Clinical symptoms are listed in Figure 3.

Thrombosis. Thrombosis generally results from intimal disruption of the vein and development of a fibrin sheath around the catheter (50, 51). Although catheter thrombosis is relatively uncommon (Table 1), if unrecognized and untreated, it may lead to the

need for catheter removal and long-term loss of a venous access site. The incidence is greater in some patients (Table 4) and the incidence of subclinical catheter thrombosis may be much greater (52–54). However, it is unknown what percentage of clots found on routine, scheduled catheter checks result in development of clinically significant thromboses.

Superior (SVC) or inferior vena cava (IVC) syndrome is a rare (incidence of 0.02–0.04/catheter year (55–57), but serious sequelae of catheter thrombosis. Our studies indicated 68% of patients with SVC or IVC syndrome had at least one prior catheter thrombosis, and nearly 40% of patients who develop catheter thrombosis will subsequently develop SVC/IVC syndrome at some time as long as they remain on HTPN (55). Intracardiac thrombosis has also been reported and is related to catheter tip position in the right atrium (57, 58). Pulmonary embolism is a very rare complication of catheter thrombosis (58–63).

Very low dose warfarin (1–2 mg daily) does not alter the PT or aPTT, but may prevent catheter thrombosis (64, 65). This may result from partial, but critical inhibition of vitamin K-dependent factors (66–68). Patients who develop thrombosis despite low-dose warfarin should be fully anticoagulated during the period they have their catheter (48, 69). Anticoagulation may require increased warfarin dose, either related to malabsorption or the vitamin K intrinsically contained in lipid emulsion (70). Long-term heparin use is not recommended because of the risk of osteoporosis (71), and it is incompatible with lipid emulsion (which has significance with the increased use of 3-in-1 emulsions) (72), although catheter flushing with heparin 100 units/ml (0.6–3 ml, depending on the catheter volume) is recommended (73, 74).

Catheter thrombosis may be treated using urokinase (Figure 3) (75, 76). If medical treatment is unsuccessful, removal and replacement in another site are necessary. Thrombosed veins may recanalize

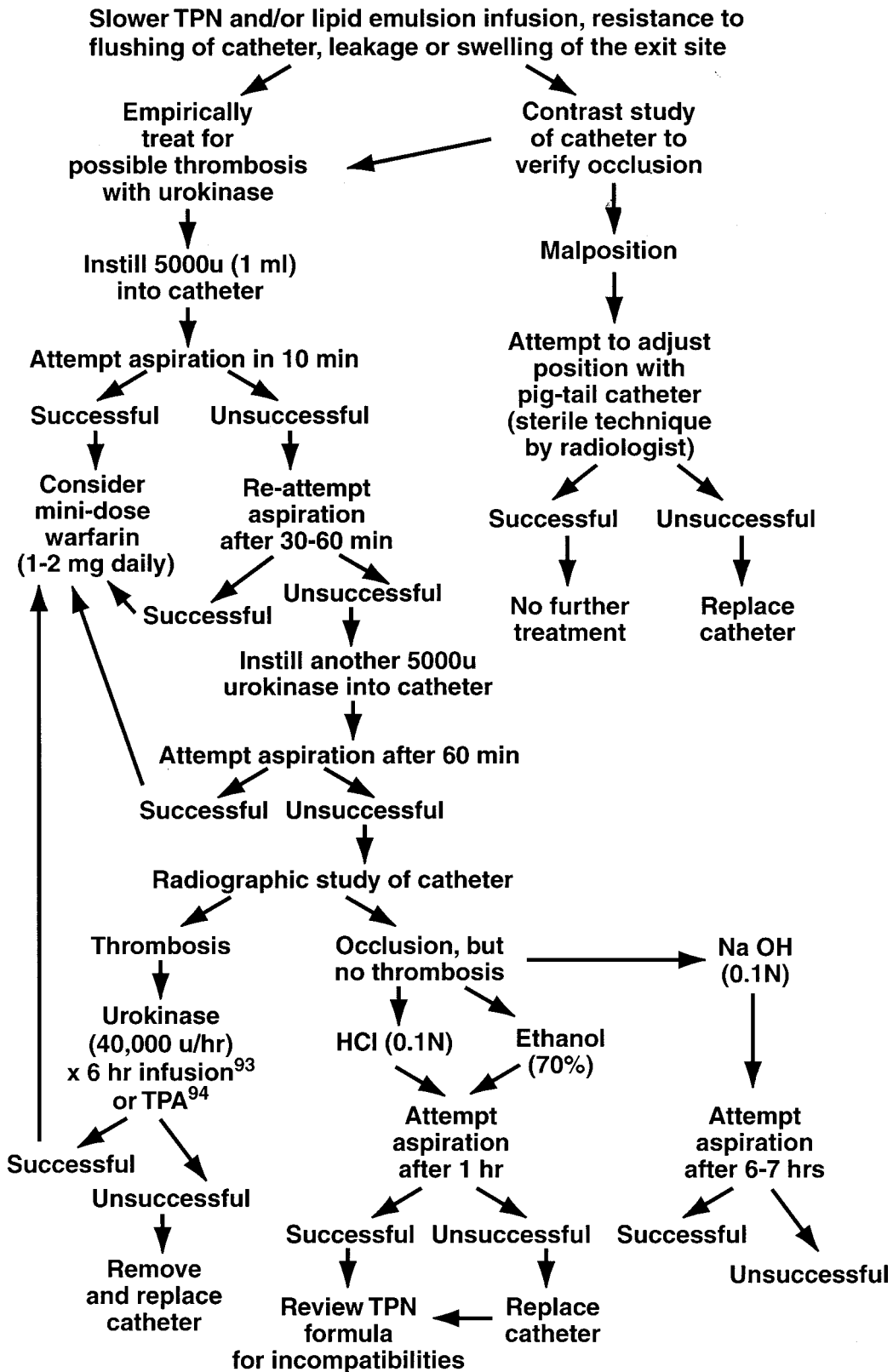


Fig 3. Suggested algorithm for the diagnosis of catheter-related occlusion (thrombotic and nonthrombotic).

TABLE 4. RISK FACTORS FOR CATHETER THROMBOSIS

| | |
|---------------------------------|-----------------------------------|
| Mesenteric vein thrombosis (57) | Protein C deficiency (72) |
| Mesenteric artery embolism (57) | Protein S deficiency (72) |
| Catheter sepsis (4,17,57,68a) | Antithrombin III deficiency (72a) |
| Antiphospholipid syndrome (69a) | Certain malignancies (73a) |
| Serum auto-antibodies (70a) | Catheter tip malposition (71) |
| | (in innominate or femoral veins) |
| Hyperhomocysteinemia (71a) | |

over several years, and it may be possible to reuse a former site for catheter placement.

Nonthrombotic Occlusion. Up to 50% of non-thrombotic occlusions may be related to mechanical problems including catheter migration or damage (76–78), precipitation related to medication–TPN incompatibilities (79–83), and lipid deposition (84, 85). Hydrochloric acid dissolves certain mineral and medication precipitates that form because of low calcium/phosphate solubility in TPN solutions used with medications that have a low pK_a in the TPN solution (Figure 3) (79–83). Sodium hydroxide has also been used, although the solution is may require up to 6–7 hr before any attempt at aspiration is made (83). Ethanol dissolves waxy lipid deposits around the catheter (Figure 3) (82, 84). It is often difficult to initially determine whether a catheter occlusion is thrombotic or nonthrombotic in origin, although lipid-based precipitates generally have a more gradual onset. Lipid occlusions also generally occur in association with 3-in-1 emulsions and not when lipids are infused separately from the dextrose/amino acid components of TPN (85, 86).

RENAL COMPLICATION

TPN-associated nephropathy is the most recent systemic complication of long-term TPN described (87, 88). Creatinine clearance declines by approximately 3.5% per year in adults (87). The etiology of this decline is unknown, but age, nephrotoxic drug use, and previous bloodstream infections are all contributing factors (87). Tubular function is also impaired in adults (87), although not necessarily in children (88). Short-term TPN leads to dramatically increased creatinine clearance, probably because of glomerular hyperfiltration, and nephromegaly may result (89, 90). Glomerular sclerosis could result over the long term.

We found no correlation between the decline in renal function and intravenous amino acid intake in either adults or children (87, 88). Excessive chromium infusion (primarily in the form of contaminants in the TPN solutions) is associated with decreased renal

function in children (91), but not adults (87, 92). Cadmium and other heavy-metal contaminants in TPN do not appear to play a role (92).

Hyperoxaluria occurs in adult HTPN patients and probably children as well (93, 94). Despite increasing the risk for nephrolithiasis, there is no correlation with renal dysfunction (93). The hyperoxaluria may be related to endogenous production from vitamin C contained in TPN solutions (94). The acidity of TPN solutions may contribute as well (87).

GASTROINTESTINAL COMPLICATIONS

Gastroparesis. Studies in normal volunteers have demonstrated that long-chain triglyceride-based emulsions will delay gastric emptying, although it is unclear whether this is clinically significant and leads to early satiety (95). The etiology for this finding is unknown. Hyperglycemia even with lipid-free TPN may also cause gastroparesis and decreased gastric and pancreatic secretion (96, 97).

Intestinal Hypoplasia. Although intestinal villus hypoplasia (not atrophy) has been well described in rodent models of TPN, it has not been observed to a similar degree in humans (98–102). Slight, but statistically significant decreases in jejunal villus height have been observed in some, although not all studies (98–101). Similarly, no decrease in villus height was seen in obese volunteers who were starved for two weeks (101, 103), or in patients with jejunal or ileal bypasses 3.5–6 years following exclusion of their intestinal segments (104). Virtually all HTPN patients eat something, and many eat considerable amounts. Therefore, the intestinal changes related to the lack of luminal nutrients would likely be of an even lesser magnitude in HTPN patients. Crypt depth remains unchanged (98–100).

Intestinal permeability to macromolecules increases during TPN and the lack of enteral nutrition, although this is unrelated to changes in intestinal morphology (98, 100). The etiology for the increase in intestinal permeability remains unknown. Some patients develop intercellular edema, although both the relationship with increased intestinal permeability

and clinical significance are speculative. There are few data to support a functional impairment of the gastrointestinal tract during TPN. Although Guedon et al observed a decrease in duodenal disaccharidase concentrations after two to three weeks of TPN (99), we found no functional deficit (98). Contrary to animal studies, TPN is not associated with intestinal immune dysfunction (105, 106).

METABOLIC BONE DISEASE

TPN-associated bone disease was first described by Shike et al (107) and Klein et al (108) in 1980. Many factors may be involved, including lifestyle and underlying disease. Its prevalence is unknown. Patients may be asymptomatic or may manifest bone pain, back pain, or fractures. Low trabecular bone density (lumbar spine), measured either by quantitative computed tomography or dual-energy absorptiometry, signify increased fracture risk. Bone biopsy following double tetracycline labeling (to determine if bone formation is decreased and if osteoid is increased) may also be useful in the diagnosis. The disease was originally characterized by transient hypercalciuria, high normal plasma 25-OHD₃, hypercalcemia, normal or low serum parathyroid hormone [although Klein et al reported normal to elevated PTH (108)], and negative calcium balance with normal serum phosphorus with increased osteoid and decreased mineralization evident on bone biopsy (109). Decreased serum 1,25-(OH)₂D₃ has also occasionally been reported (109).

Hypercalciuria may reflect the cycled nature of home TPN, increased bone resorption, excessive amino acids infusion, vitamin A toxicity, or hyperinsulinemia (110–112). It may be reduced by increasing the phosphorus concentration in the TPN (113), although one must be careful to avoid precipitation with calcium. Most current adult TPN solutions contain a standard phosphate concentration of 10–15 mmol/liter (usually 30–45 mmol/day), which is short of that recommended based some balance studies (114) and that used by Wood et al to treat hypercalciuria (113).

Chronic acidosis has also been associated with hypercalciuria and metabolic bone disease (115–118), although one of the treatments (acetate) has been associated with inhibition of osteoblast proliferation *in vitro* (119). However, other studies have shown that correction of chronic acidosis with acetate (replacement of 160 mmol Cl with 160 mmol Ac) leads to decreased hypercalciuria (120).

Aluminum toxicity, manifested by elevated plasma, urine, and bone aluminum concentrations and low turnover bone disease was found to be a significant contributor to the development of TPN-associated osteomalacia (121, 122). Reduced bone formation and reduced serum 1,25-(OH)₂D₃ is characteristic of aluminum bone toxicity (121–123). Significant aluminum contamination was found in the casein protein hydrolysate, and in mid-1981, these solutions were discontinued and crystalline free amino acid-based formulas were substituted. Studies showed this resulted in increased bone formation (123, 124). Reduction in the degree of aluminum contamination was also associated with increased serum 1,25-(OH)₂D₃ (123). While aluminum contamination has been reduced significantly, other TPN components including sodium phosphate, calcium gluconate, and multivitamins still contain rather large concentrations of aluminum although their contribution to the overall TPN solution may be rather small (125). Unfortunately, low bone formation characterized by low bone mineral content continues to be a problem in some, but not all HTPN patients despite the lack of significant aluminum exposure (124, 126–128).

Other potential causes of metabolic bone disease in patients requiring home TPN include the underlying disorder (127, 130) (eg, dehydration, primary hyperparathyroidism, hypoparathyroidism—often related to magnesium deficiency from chronic diarrheal losses, vitamin D malabsorption, cytokine activity) and medication-induced osteopenia from corticosteroids, methotrexate, cyclosporin, or tacrolimus used in the therapy of the underlying disorder. Plasma fluoride concentration has been shown to correlate significantly with bone mineral density in children requiring long-term home TPN, although there are no studies of fluoride supplementation in home TPN patients (131).

Shike et al suggested vitamin D contained in the multivitamin preparations used in TPN may have a toxic effect on bone (107, 132). Hypercalciuria decreased in three patients who had vitamin D withdrawn from their TPN solutions, and osteomalacia improved in one of the patients who had follow up bone biopsies (107). However, the patients may have had secondary hyperparathyroidism prior to beginning TPN, where bone mineralization is impaired, but osteoid formation is increased (133). In a subsequent study, Shike et al found significant aluminum contamination was present in these patients' TPN (based on the likelihood at least some patients received casein hydrolysate during their early days of TPN), although

only 3 of 12 had positive aluminum bone staining (132). Bone biopsies of these patients showed reduced osteoid and total bone volume (consistent with decreased bone matrix formation and normal mineralization) with normal resorption activity, although osteoid and mineralization were reportedly normal in patients with positive aluminum staining. This contrasts with the previously described studies where osteoid was increased and mineralization decreased in association with low serum vitamin D and PTH. In the Shike study, serum 25-OHD₃, 1,25-(OH)₂D₃, calcium, PTH were all normal, although the serum aluminum concentration was elevated (132). In addition, a decrease in the osteoid area with a concurrent increase in bone mineralization was described in patients who were switched from casein-based amino acids to crystalline amino acid (123).

Others have found a significant correlation between serum 1,25-(OH)₂D₃ and biochemical measures of bone formation in patients who did not receive significant aluminum, suggesting that increased serum 1,25-(OH)₂D₃ may stimulate bone formation, rather than depress it (134). However, long-term (4.5 years) vitamin D withdrawal in patients with depressed serum PTH and 1,25-(OH)₂D₃ only has been associated with a significant increase in lumbar bone mineral density and normalization of both PTH and 1,25-(OH)₂D₃ (135). TPN-associated bone disease and the role of vitamin D remain poorly understood.

HEPATIC DISEASE

TPN-associated liver was first described in 1971 (136). The prevalence of end-stage liver disease varies between 15% and 40% in the adult population and is greater in neonates (137, 138). Since then, the association between hepatic aminotransferase abnormalities and TPN has been well documented, and three distinctive morphologic abnormalities in the liver have been described. Liver test abnormalities are nonspecific and insensitive indicators for specific hepatic morphologic lesions (139) but are often elevated within four to seven weeks of TPN initiation and may remain as long as TPN is continued (140, 141). In adults, elevation in serum bilirubin is unusual (142) but is being observed with increased frequency (AL Buchman, L Howard, D Kelly, unpublished observations, 1998). Alkaline phosphatase elevation may be related in part to metabolic bone disease, and not liver disease alone (108). Liver *function* during TPN has not been evaluated in humans.

Morphologic abnormalities in adults include steatosis (macro- and microvesicular), cholestasis, and phospholipidosis. TPN-associated liver disease in adults usually manifests as hepatic steatosis or steatohepatitis (139, 143–145), although this may be progressive with subsequent development of cirrhosis and hepatic failure (146–152). Dextrose overfeeding was once a common cause of benign hepatic steatosis (although severe steatosis with hepatomegaly may be painful) in an era of overfeeding when patients were routinely provided with 50–60 kcal/kg/day (153, 154). This has become less common when currently accepted norms of 25–40 kcal/kg/day are used.

Since the widespread use of lipid emulsions became popular in the early 1980s, essential fatty acid deficiency is extremely uncommon as long as patients receive a minimum of 2–4% of their calories as linoleic fatty acid (eg, 4–8% of daily calories as lipid emulsion) (155–157). A triene-tetrene ratio >0.4 (158), or a low plasma linoleic fatty acid concentration is indicative of biochemical fatty acid deficiency and can develop as soon as two weeks following withdrawal of lipids (154). Clinical signs may include skin rash, neuropathy, hepatosplenomegaly, and thrombocytopenia.

Acquired carnitine deficiency had been proposed to cause TPN-associated hepatic steatosis. However, carnitine supplementation does not improve hepatic aminotransferase abnormalities, the degree of hepatic steatosis, or lipid utilization in TPN-requiring patient (159, 160). Despite these data, carnitine supplementation is routinely provided to patients in some institutions. Carnitine can be synthesized from the amino acids lysine and methionine contained in the TPN solutions.

Low plasma free choline has been observed in patients that require TPN (145, 161–164). Significant correlations exist between both hepatic aminotransferase concentrations and degree of hepatic steatosis and the plasma free choline concentration (145, 164). Choline is necessary for very low density lipoprotein (VLDL) synthesis, and when insufficient VLDL production occurs, defective triglyceride transport from the liver results (165, 166). Massive lecithin (13% choline) doses lead to a significant increase in plasma free choline concentration and a corresponding decrease in hepatic steatosis in a study of HTPN patients, although both remained abnormal (145). A recent study used intravenous choline to restore plasma free choline concentration to normal and ameliorate hepatic steatosis (161). A double-blind, placebo-controlled trial of choline-supplemented

TPN on hepatic morphology has confirmed the findings of the previous open-labeled study. It appears choline may be an essential nutrient for TPN-dependent patients, although it is not currently available commercially (167).

Frank cholestasis, manifested morphologically in ballooning of hepatocytes, Kupffer cell hyperplasia, and bile duct plugging is uncommon in adults, although the incidence may be increasing (AL Buchman L Howard, D Kelly, unpublished observations, 1998). Patients with the shortest residual intestine (146–148), and those who receive moderate and larger doses of lipid emulsion (>1.0 g/kg/day) (148, 168) appear particularly at risk. Hepatocellular carcinoma, possibly related to choline deficiency has also been reported (169–171). Whether or not manganese toxicity occurs and contributes to cholestasis is unclear (172, 173). Phytosterolemia (from plant sterols contained in lipid emulsion) associated with higher doses (> 1.4 g/kg/day) of lipid emulsion has been reported in children, although not in adults, and the serum concentration of phytosterols did not necessarily correspond to the amount of lipid infusion (174). In three of the five patients with severe hepatic dysfunction, total serum bilirubin and AST concentrations decreased in parallel with a decrease in the plasma phytosterol concentration, which followed a decrease in the volume of lipid infused. Phospholipidosis has also been rarely described following prolonged infusion of lipid emulsion (175).

There are few treatment options for TPN-associated cholestasis. Phenobarbital and antibiotics such as gentamicin are useless (176, 177). Some studies have shown ursodeoxycholic acid (UCDA) at a dose of 10–45mg/kg/day to significantly improve cholestasis in preterm infants, while others have shown less impressive results (178, 179). Data in adults is limited to 10 patients who had generally limited improvement when treated with UCDA (6–15 mg/kg/day (180, 181). Cholecystokinin (0.04 μ g/kg twice a day) injections were associated with numerically, but not significantly, lower serum direct bilirubin concentration in neonates that required TPN (182). This has not been studied in adults. Combined liver–small intestinal transplantation may be the only potentially viable option for a patient with TPN-associated hepatic failure. It is important to exclude other, non-TPN-related and potentially treatable causes of liver disease.

BILIARY DISEASE

Home TPN patients are at risk for both acalculous and calculous cholecystitis (183). Acalculous cholecystitis occurs because of decreased gallbladder emptying related to the decreased release of cholecystokinin (CCK) on the basis of insufficient oral food intake (184, 185). Narcotic use, bile stasis, and increased bile lithogenicity may also be contributing factors (184–186). Patients may develop massive gallbladder dilation and require percutaneous cholecystostomy for drainage. Gallbladder dysmotility and abnormal emptying may result in false positive iminodiacetic (IDA) hepatic scintigraphy (187–189), although intravenous morphine may improve scan specificity (189). Patients should eat on a daily basis, even if they are completely TPN-dependent, in order ensure adequate gallbladder emptying and possibly prevent development of cholecystitis.

Biliary sludge developed in 50% of patients following four to six weeks of TPN and in virtually 100% after six weeks of TPN (190, 191). Some of these patients ultimately develop gallstones. Messing et al also showed sludge resolved in all patients following four weeks of enteral/oral refeeding (190). Gallbladder stasis may be the most important risk factor, similar to acalculous cholecystitis (192, 193). However, most stones are calcium bilirubinate in composition, rather than cholesterol (194–196). This suggests the possibility of a chronic infectious process, although the exact etiology for pigmented stones is uncertain (197).

CCK injections have been used to induce gallbladder contraction and reduce the prevalence of biliary sludge (198–200). However, this treatment is not universally successful and has been associated with cholecystitis, nausea, and flushing in some patients (199–201). Rapid, high-dose intravenous amino acid infusions (0.3–2.1 g/min 0.12–0.14 g/min for cyclic home TPN patients) have also been used to stimulate gallbladder contraction (202, 203). However, this approach is clinically impractical and lower infusion rates are not very successful (203). Relatively rapid infusion of lipid emulsion (10% at 100 ml/hr for 3 hr) also stimulates gallbladder contraction and may be useful preventative therapy (204, 205). This may be mediated via CCK release (206). Intravenous chenodeoxycholate has shown promise in the prairie dog model for the prevention of calcium bilirubinate gallstones, although it has not been studied in humans (207). The prevention of calculous cholecystitis still remains suboptimal. The best and least expensive

means to prevent cholecystitis in HTPN patients is to simply encourage patients to eat.

CONCLUSION

Patients who require long-term TPN have impressive survival when compared with small bowel transplantation. However, both survival and morbidity are significantly affected by potentially serious complications from this therapy. These complications may result from nutrient deficiencies or excesses and/or mechanical problems associated with the delivery system. Infectious complications, the most common, are often related to insufficient education provided to the patient, which usually leads to suboptimal catheter care. The etiology and prognosis of other complications, such as the metabolic bone disease, nephropathy, and hepatobiliary disease are more obscure, and are therefore challenging to manage appropriately. It is hoped, ongoing and future investigation will lead to improved quality of care.

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