PERGAMON

European Journal of Cancer 37 (2001) 1649–1658

European Journal of Cancer

www.ejconline.com

Paediatric Update

Indwelling lines and nutrition

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Received 23 January 2001; accepted 1 March 2001

1. Introduction

Survival rates after childhood cancer have been steadily increasing due to the use of multimodal, intensive treatment strategies. Further intensification of cytotoxic therapies is leading to profound, prolonged neutropenic episodes lasting several weeks and frequent use of peripheral stem cell rescue following myeloablative chemotherapy. Supportive care has therefore become an even more important factor in assuring patient's progress towards cure and this 'Update' concentrates on the issues surrounding central vascular access and nutrition.

2. Central venous access

Central venous lines were introduced in the 1970s [1,2] and are now widely used for the treatment with cytotoxic agents, antibiotics, total parenteral nutrition, blood products and blood sampling. Like almost any medical intervention, however, these devices are not problem-free. Infection, either of the exit site or of the catheter lumen itself, is a common, potentially lethal complication. Thrombosis of the catheter lumen or of the veins close to the catheter can occur and is probably underreported [3]. In addition, central venous catheters can fragment and dislodge, a diagnosis only made if there is a high level of clinical suspicion [4,5]. Accidental removal of tunnelled external central venous lines occurs in up to 8% of cases [6,7]. Reducing complications by choosing the most appropriate central venous catheter for each clinical situation and optimising its maintenance care are crucial, if the benefit of the device is to be maximised.

2.1. Choosing the appropriate central venous catheter

The minimum number of catheter lumens required to deliver the treatment schedule whilst allowing for the level of anticipated supportive intravenous care are prime considerations. A flow-diagram describing a possible decision-making pathway is shown in Fig. 1. Central venous catheters with multiple lumens are associated with increased morbidity [8] and additionally, the smaller anatomical structures of young children limit the overall dimension of the catheter. As a 'rule of thumb', the lowest number of lumens associated with the smallest overall catheter diameter should be selected [9].

The risk of infection is significantly reduced in fully implantable subcutaneous ports (around 0.5 per 1000 catheter days versus around 2.0 per 1000 catheter days in tunnelled, cuffed silastic catheters [10,11]). Furthermore, implantable subcutaneous ports are associated with a smaller risk of intraluminal thrombosis (around 0.5 versus 2.3 episodes per 1000 catheter days) than tunnelled, cuffed silastic catheters [12–15]. Although cuffed silastic catheters have a number of potential problems which include increased infection risk and the resulting treatment costs, imposed restrictions in physical activities, effects on the body image in older children and increased risk of accidental removal of the catheter, fully implantable ports are not always the preferred first choice [11]. Possibly because clinicians often overestimate the potential need for more than a single lumen which in many cases can be overcome in older children by using an implantable double chambered port. Additionally, a single chamber port can be upgraded, for example at the time of bone marrow transplantation, by inserting a percutaneous tunnelled central venous line at a separate site. This strategy avoids the increased risk of thrombosis associated with the manipulation of the existing central venous catheter [16]. Peripherally inserted central venous catheters (PICC lines), especially double lumen, are often not small enough in size to be

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PII: S0959-8049(01)00208-8

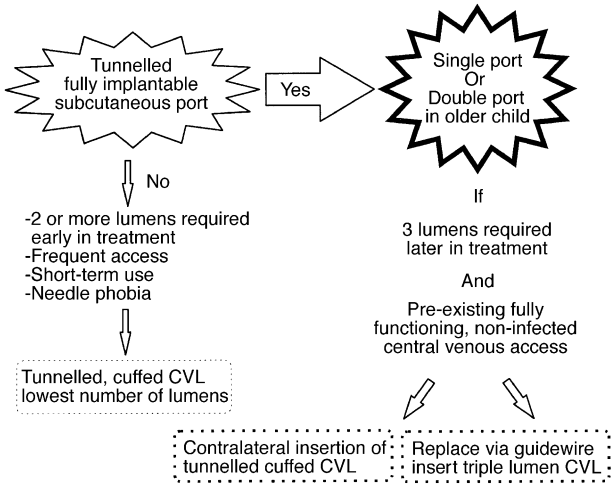

Fig. 1. Choosing the appropriate central venous catheter. CVL, central venous line.

suitable for young children. Adolescents and young adults can benefit from PICC lines as a short-term measure, e.g. during infective episodes in the absence of peripheral venous access, but their role has not been fully established [17].

2.2. Insertion techniques of central venous access devises

Originally, central venous lines were inserted surgically using an open, cut-down procedure. In recent years, it has become more common to use a percutaneous, radiological approach and mobile image intensifier or ultrasound guidance [18,19]. In some cases, angiography with fluoroscopic guidance may prove invaluable [19] and should be available in case of difficulties in gaining venous access. The catheter tip should reach the superior vena cava or the right atrium, a position associated with the least thrombotic complications [20].

A large, comparative single institution analysis of a radiological or surgical (open cut-down) placement of 253 tunnelled central venous (Hickman) lines in adult patients showed that reliable placement was superior using a radiological approach, and was associated with significantly fewer infections (around 1.9 versus 4.0 per 1000 catheter days, respectively) [19]. It has also been shown that complication rates, especially pneumothorax is related to the inexperience of the operator and a minimum of 30 tunnelled central venous line insertions has been recommended before undertaking the procedure unsupervised [21]. The incidence of pneumothorax can be further reduced by a more lateral approach via the axillary vein [22] or via the internal jugular vein, a preferable route in children [18]. Worryingly, in one study, half of adult surgical central venous line insertions were performed 'out of hours' due to pressures on operating theatre time [19], a suboptimal situation associated with a higher level of complications. In view of the need for a general anaesthetic to insert a central venous catheter in children it is important to have dedicated theatre time, e.g. 'lines lists' supported by interventional radiologists, surgeons able to use radiological techniques and nursing staff that share a common interest in improving the service and minimising the need for out of hours, emergency operations.

2.3. Infection and central venous catheters

Infection is the commonest complication of central venous access especially in the external tunnelled central venous line (around 2.2 per 1000 catheter days [10,11]), a situation exacerbated by treatment-related episodes of neutropenia. The following actions are known to reduce early infection, presenting either as bacteraemia within the first few postoperative days or an infection of the exit site: (a) meticulous skin care during the catheter insertion using alcohol based chlorhexidine or betadine [23], (b) absence of fever at the time of insertion and (c) avoidance of a potential source of bacteraemia via any second surgical procedure performed at the time of insertion and (d) radiological insertion by an experienced team [19]. Exit site infections can inhibit the fibrotic process around the Dacron cuff of an external central venous line which normally takes up to 4 weeks to develop and can therefore increase the risk of accidental removal.

Techniques for coating the central venous catheter with antibiotics, e.g. silver–teicoplanin complexes, may have been recently introduced to try to reduce the adherence of bacteria to the catheter [24], but it is difficult to envisage how colonisation following insertion could be prevented once the catheter becomes coated by a layer of fibrin, albumin and platelets. Intravenous antibiotic prophylaxis aimed at preventing Gram-positive infections is presently not recommended [9] because of the worrying increase in vancomycin-resistant enterococci [25].

Fig. 2 illustrates a pathway to aid the clinical diagnosis and treatment of a febrile episode in an oncological patient with a central venous access. Clinical signs of infection can be more subtle during neutropenic episodes. A high level of clinical suspicion, frequent reviews of the clinical development and the knowledge of locally prevailing pathogens — including their sensitivity/resistance spectrum — are vital in any institution to minimise morbidity and mortality. Table 1 shows central venous line-related pathogens isolated from paediatric haematological and oncological patients at the Birmingham Children's Hospital, United Kingdom, over a 12 month period. Most catheter-related infections can be cured with appropriate antibiotics [10], but tunnel infections are particularly difficult to clear possi-

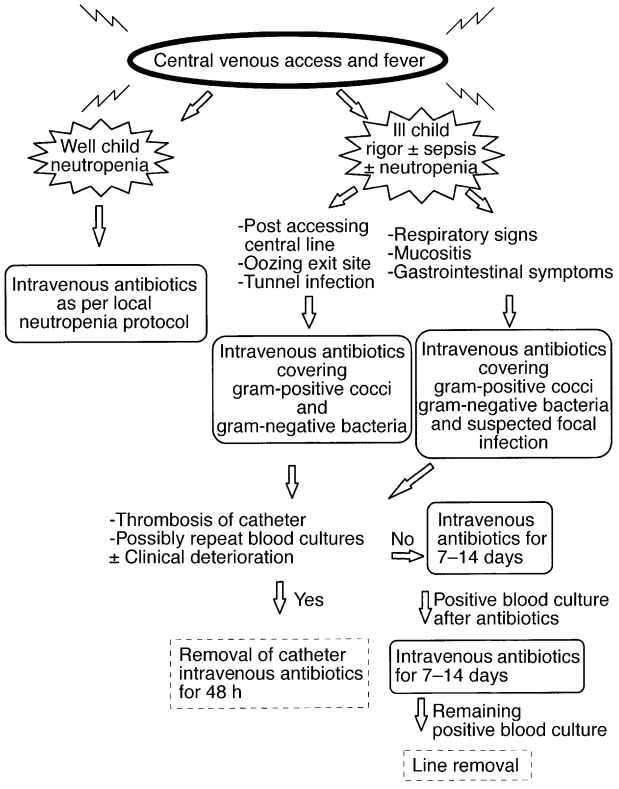

Fig. 2. Treatment algorithm for central venous catheter-related infections.

bly due to poor antibiotic penetration [26,27]. Interruptions and delays in the planned treatment schedule secondary to serious infections may have negative effects on the outcome of the child's cancer treatment.

2.4. Thrombotic events associated with central venous access

Thrombotic events are a frequent complication of central venous lines causing intraluminal occlusion and affect 0.23–2.21 per 1000 catheter days in external tunnelled central venous lines and 0.3–0.53 per 1000 catheter days in implanted ports [12–15]. Extraluminal thrombosis of the veins close to the catheter is a less frequent problem, although underreported unless venograms or ultrasonography are used for surveillance [3,20,28].

Asymptomatic thrombosis of the catheter lumen should be treated with the instillation of a fibrinolytic agent (urokinase or streptokinase). A 'push–pull' action should be used to maximise mixing of the solution without ballooning the line and it should be withdrawn within 24 h [9]. Alternatively, low dose urokinase (40 000 U urokinase per hour at a rate of 8 ml per hour) can be given as continuous infusion until the thrombus is resolved and can be successful following failed urokinase boluses [29,30]. Additionally, any unexplained increase in pressure causing a 'stiffening' of the central venous catheter should be treated with a fibrinolytic agent [30]. A predisposition to catheter-related thrombosis is sometimes present (Table 2). Weekly flushing of the external central venous line with heparin is a useful preventative measure [31], although some studies suggest similar benefits from isotonic saline [32]. Although the use of low-dose warfarin has been shown to prevent repeated events of catheter thrombosis [33], it is not advisable in patients who may be or may become thrombocytopenic. The occurrence of a line occlusion during a catheter-related bacteraemic episode often requires removal of the line, since the underlying pathological processes may exacerbate each other.

An apparent occlusion of a central venous catheter, either an external tunnelled central venous line [5] or a subcutaneous port [4], not responding to fibrinolytic treatment or associated with cardiovascular and respiratory distress requires immediate investigation to exclude fragmentation or disconnection of the device with or without associated embolisation. Catheter embolisation can be easily missed because it is rarer (0.1–1% of cases) than catheter malfunction and may be symptomless [4,5]. Retrieval of fragmented and embolised central venous catheters requires a multidisciplinary approach using an interventional radiologist or cardiologist and imaging facilities in the operating theatre.

Table 1
Central venous catheter related bacteraemia and fungaemia in paediatric haematology and oncology patients at Birmingham Children's Hospital, United Kingdom from October 1999 to September 2000

Species	Episodes (%)	Species	Episodes (%)
Gram-positive	63	Gram-negative	28
Coagulase-negative staphylococcus	45	*Acinetobacter* spp.	4
Staphylococcus aureus	12	*Escherichia coli*	4
Micrococcus spp.	4	*Pseudomonas* spp.	4
Others	2	*Stenotrophomonas maltophilia*	3
		Sphingomonas spp.	3
Yeasts	3	others	10
Candida spp.	2		
Rhodotorula spp.	1	Multiple Organism	6

spp, species.
Data from Dr Gray, Department of Microbiology, Birmingham Children's Hospital.

Table 2
Predisposition to central venous catheter thrombosis and possible preventative measures

Cause	Action
Acute lymphoblastic leukaemia (induction)	Insertion following induction
Catheter-related bacteraemia	Early and appropriate treatment of infection
Severe dehydration	Fluid balance
Small vessel size	More central access, thinner catheter
Radiotherapy field	Use contralateral side
Multiple insertions of central lines	Imaging of vasculature before insertion
Extravascular pressure by tumour mass	Use contralateral side

2.5. Patient information

Although the insertion of a central venous catheter is eagerly awaited by the patient and their family, it is commonly associated with significant anxiety because of the family's responsibility to help care for the line and because of its effect on daily activities. Repeated, informed discussions with trained staff, other patients and the use of written information are both important. The booklet 'Wiggly's World', a user-friendly cartoon designed for children, explains external central venous lines and also introduces some concepts about cancer and treatment-related side-effects [34]. Independence and a significant improvement in the quality of life benefiting the whole family can be achieved by teaching the parents how to flush the external central venous line safely at home.

2.6. Controversies and future avenues

The most appropriate way of using intravenous antibiotics to treat a central venous catheter infection is still controversial. What is the most beneficial length of contact time and concentration of antibiotic within the catheter? A bolus injection of the antibiotic will lead to a short contact time with bacteria adhering to the fibrin sheath lining of the catheter lumen and whilst an infusion has been shown to be more beneficial, a continuous 24-h infusion results in a lower antibiotic concentration in the catheter lumen [35,36]. 'Locking' the antibiotic into the catheter is useful in a stable patient free of symptoms or signs suggestive of sepsis.

Twenty to thirty percent of central venous catheters are not salvageable following infections [37]. It is presumed that the bacteria colonise the fibrin sheath surrounding the catheter and its lumen. If this speculation is true, dissolving the fibrin sheath with urokinase as well as antibiotics should improve catheter salvage. Initial studies suggested a benefit to the use of urokinase [38], but these findings could not be confirmed in small randomised studies [39].

Catheter occlusion can be caused by precipitation of drugs, calcium phosphate crystals or lipids and may therefore not respond to thrombolytics. Administration of 0.1 N hydrochloric acid, in addition to heparin or streptokinase, has been used successfully in such circumstances [40,41]. Temporary febrile reactions were common, but no serious complications were observed. Sodium bicarbonate (1 ml of 1 mEq/ml) or ethyl alcohol (1 ml of 70% ethyl alcohol) have also been described as useful agents to clear chemical precipitations [42,43]. The treatment of infected central venous devices with antibiotics and hydrochloric acid and management of thrombosed lines with hydrochloric acid and streptokinase has been reported to extend their life span [6].

3. Nutrition

Up to one-third of paediatric cancer patients may be malnourished at diagnosis [44,45]. At presentation, malnutrition is more frequently associated with metastatic disease and solid tumours, particularly Ewing's sarcoma, Wilms' tumour, neuroblastoma, advanced lymphoma and head and neck tumours than with leukaemia [46,47]. Malnutrition develops in a further 40–80% of children during therapy [48] and cachexia is most commonly iatrogenic and secondary to intensive chemotherapy [49] leading to a reduced oral energy intake relative to the energy expenditure. The multifactorial causes of malnutrition are depicted in Fig. 3. Progressive weight loss, due to a reduction in adipose tissue, is also associated with an increased protein turnover, breakdown in muscle tissue and a decrease in protein concentrations [50–52].

These complex metabolic changes can lead to a reduced tolerance to multi-agent therapy, inadequate metabolism of chemotherapeutic agents, an impaired immune response, reduced levels of well-being and physical activity [44,53,54]. The effect of cachexia on overall outcome are less clear [44,55,56]. Although the importance and benefits of maintaining an adequate nutritional status throughout treatment is universally accepted, there is no simple, easy definition of a child at risk of malnutrition and constant monitoring and surveillance are mandatory [57,58]. Few institutions, even now, have 'nutritional care teams' that monitor the daily and weekly nutritional status of their patients.

3.1. Definition of malnutrition

There is no agreed, clinically useful and reliable definition of malnutrition. The commonly used 'weight for height ratio' is an index of body shape. Using the percentage of weight for height (measured weight expressed as percentage of ideal weight for height) correlates with lean and fat tissue mass, but can still lead to an underestimation of cachexia [57]. A study of 62 newly diagnosed children with malignant disease found 27% with severe malnutrition, according to mid-arm circumference and skinfold thickness, even though height and weight indices were within normal limits [45]. Body mass index (weight/height^2) is problematic in a childhood population in which the exponent changes with age. In addition, growth, body composition and puberty can be significantly different from the normal population [59]. To determine body composition, measurements of mid-upper arm circumference, triceps and biceps skinfold thickness are useful [60]. Measurements below the 5th or 10th centile on reference population charts have been considered to indicate malnutrition [58,61].

Clincally useful biochemical investigations associated with the catabolic state of malnutrition include measurement of various serum proteins, e.g. transferrin, albumin and retinol binding protein [62,63]. However, some serum proteins are 'acute phase reactants' and their levels are influenced by fever and infections as well as hepatic function. Therefore, levels have to be interpreted in the clinical context [62,63]. Reduced levels, however, are usually indicative of a catabolic state.

3.2. Enteral nutrition

Nutritional support via enteral feeding is the most physiological route and maintains a trophic effect on the gut mucosa. Enteral feeding allows a more normal lifestyle, is cost-effective and is associated with less toxicity than total parenteral nutrition. It should be the first choice for nutritional support [44]. An algorithm for a possible nutritional support pathway is shown in Fig. 4.

Inadequate caloric intake, chemotherapy or infection-related damage to the gut mucosa and poor acceptance of a fine bore Silk nasogastric tube are common causes for a failure of enteral nutritional support. The daily placement of a nasogastric tube was an acceptable alternative for older teenagers [61]. Endoscopically-placed gastrostomy tubes are more useful if feeding is expected to be prolonged [64] or if severe oro-pharyngeal mucositis is anticipated. Treatment-associated nausea and gastrointestinal mucositis limit the infused volume of enteral feeds. In a study by den Broeder and colleagues [61], and despite efforts to maximise the tolerability of the feed, only 80% of the required volume was achieved. As a consequence, the nutritional status improved over the 10 week observation period in children receiving standard formula feeds (1 cal/ml), but did not normalise. In comparison, children being supplemented with energy-enriched feed (e.g. 1.5-fold higher energy content) tolerated the same volume of feed and achieved their calculated energy requirements. Diarrhoea, an early phenomenon after initiation of enteral feed supplementation commonly seen in younger patients [64], was not a significant problem with the energy-enriched feed [61].

Recent studies have investigated the feasibility of 'anticipatory' enteral feeding in children likely to develop gastrointestinal toxicity secondary to intensive chemotherapy or bone marrow transplantation. In a

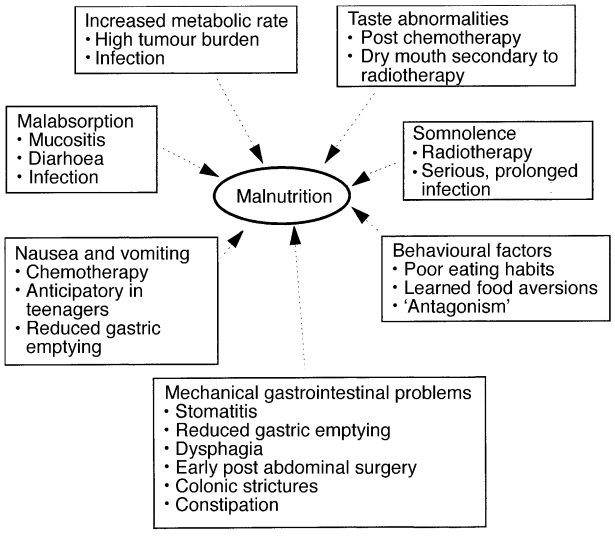

Fig. 3. Multifactorial causes of malnutrition in paediatric cancer patients.

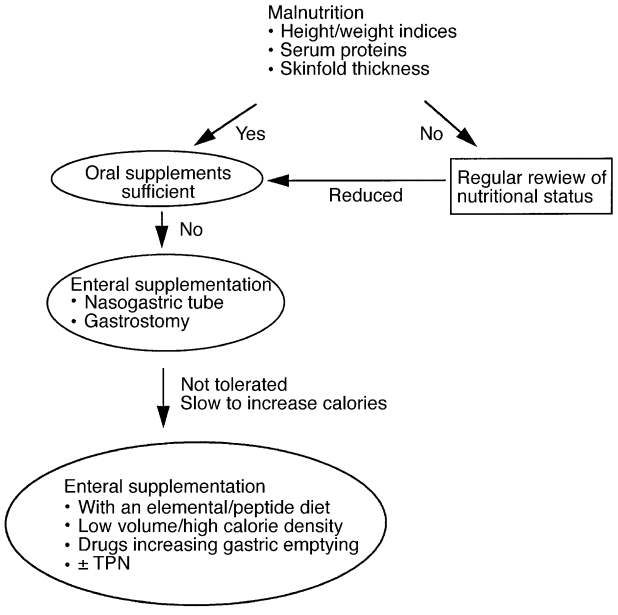

Fig. 4. Algorithm for nutritional support. TPN, total parenteral nutrition.

pilot study [65], the need for total parenteral nutrition was avoided in 65% of children undergoing intensive chemotherapy or bone marrow transplantation and the enteral feeding (glutamine-containing feed) via nasogastric tube was acceptable to the families and children. Children that did not maintain adequate oral caloric intake continued to fail to gain weight once total parenteral nutrition was added. Weight gain was observed in 41% of children, all fully enterally fed. No complications of nasogastric tube feeding were attributed to neutropenia or thrombocytopenia. The suitability of enteral feeding post bone marrow transplantation is also supported by a non-randomised trial [66]. Although further prospective, large scale studies are required, it does appear that the tolerability of enteral feeding is underestimated and, as a consequence, is underused.

3.3. Total parenteral nutrition

Although total parenteral nutrition, available for over 20 years, remains an extremely useful treatment strategy that allows nutrition, bypassing a non-functioning gastrointestinal tract, it is fraught with frequent, serious and potentially irreversible side-effects, e.g. fluid overload, increased rate of catheter-related infection, hyperglycaemia and hepatic dysfunction [67–69]. A complicated and expensive support system is required to deliver 'safe' total parenteral nutrition.

Total parenteral nutrition can maintain but rarely improves nutritional status [44,70]. Overall, total parenteral nutrition should be used, in addition to enteral feeding, during the acute phase of gastrointestinal disturbance in patients that are severely malnourished or expected to absorb only small amounts of their caloric requirements via their gastrointestinal tract [44,71].

3.4. Controversies and future avenues

Diarrhoea associated with enteral feeding is thought to be secondary to secretion of water and electrolytes in the colon [72] and can be a problem in up to 30% of patients [64]. The secretory effect can be abolished experimentally by an increase of short-chain fatty acid concentration in the caecum [72], with an additional trophic effect on the colonic epithelium and a possible reduction in bacterial translocation in the colon [73]. The effective enteral delivery of short-chain fatty acids is still a problem because of degradation in the small intestine. New technology is urgently needed.

Radiotherapy- and methotrexate-induced damage of the gut mucosa can be reduced in rat models by oral glutamine supplements [74,75]. A recent study has investigated the beneficial effects on oral mucositis during and after chemotherapy of low dose oral glutamine in patients that had experienced mucositis during earlier courses of chemotherapy [76]. The duration of mouth pain was reduced by 4.5 days and there was an overall reduction in pain severity.

Total parenteral nutrition, used alone, causes gut mucosal atrophy because it is deficient in specific enteral nutrients [77]. Experiments in rats show that mucosal atrophy can develop within 7 days of starting total parenteral nutrition. The enteral use of glutamine — the preferred energy source for the gut — and short chain fatty acids helped to reverse mucosal atrophy. It also reduces bacterial translocation via the gut mucosa, resulting in a lower incidence of central venous catheter infections [78]. Although glutamine-supplemented total parenteral nutrition is reported to prevent further deterioration of gut permeability, leading to a lower rate of infections and a shorter hospital stay after bone marrow transplantation, no effect on mucositis was detectable [79,80]. Oral supplementation of glutamine after bone marrow transplantation in adults does not always 'translate' into a shortened hospital stay or improved clinical indices [81–83]. Current clinical studies are investigating the possible benefits of oral glutamine supplementation in bone marrow transplant patients receiving total parenteral nutrition.

4. Conclusion

Intensification of paediatric oncological and haematological treatment protocols requires the prolonged use of central venous access devices in an immunocompromised patient. Attention to detail, use of locally established guidelines, education of the patient and their family, awareness of principles of hygiene and a team of well trained staff are factors that will help to minimise the side-effects of central venous access devices. Fully implanted central venous ports are associated with the lowest rate of complications (infection and thrombosis) and should be the central venous access device of choice in most children.

Although malnutrition is a well recognised problem in child cancer patients, its effect on overall outcome is still uncertain. The risk of malnutrition developing secondary to intensive multimodality treatment schedules can be predicted using dietetic algorithms focusing on mid-upper arm circumferences, biochemical markers, caloric intake and the proposed treatment regimen. Enteral routes of nutritional support are associated with less complications and recent studies suggest that they may be particularly useful in bone marrow transplant patients.

References

1. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. *Surg Gynaecol* 1973, **136**, 602–606.

2. Hickman RO, Buckner CD, Clift RA, Sanders JE, Stewart P, Thomas ED. A modified right atrial catheter for access to the venous system in marrow transplant recipients. *Surg Gynaecol Obstet* 1979, **148**, 871–875.
3. Haire WD, Lieberman RP, Lund GB, Edney JA, Kessinger A, Armitage JO. Thrombotic complications of silicone rubber catheters during autologous marrow and peripheral stem cell transplantation. *Bone Marrow Transplant* 1991, **7**, 57–59.
4. Monsuez JJ, Duoard MC, Martin-Boyer Y. Catheter fragments embolization. *Angiology* 1997, **48**, 117–120.
5. Rubenstein RB, Alberty RE, Michels LG, Pederson RW, Rosenthal D. Hickman catheter separation. *J Parent Nutr* 1985, **9**, 754–757.
6. Tobiansky R, Lui K, Dalton DM, Shaw P, Martin H, Isaacs D. Complications of central venous access devices in children with and without cancer. *J Paed Child Health* 1997, **33**, 509–514.
7. Dawson S, Mohan KR, Smith S, Rothney M, Ahmed K, Barr RD. Right atrial catheters in children with cancer: a decade of experience in the use of tunnelled, exteriorised devices at a single institution. *Am J Ped Hematol Oncol* 1991, **13**, 126–129.
8. Henriquez HF, Kanny-Jones R, Knoll SM, Copes WS, Giordano JM. Avoid complications of long-term venous access. *Am Surg* 1993, **9**, 555–558.
9. British Committee of Standards in Haematology. BCSH, guidelines on the insertion and management of central venous lines. *Br J Haematol* 1997, **98**, 1041–1047.
10. Severien C, Nelson JD. Frequency of infections associated with implanted systems vs cuffed, tunnelled silastic venous catheters in patients with acute leukaemia. *Am J Dis Child* 1991, **145**, 1433–1438.
11. Ingram J, Weitzman S, Greenberg ML, Parkin P, Filler R. Complications of indwelling venous access lines in the pediatric hematologic patient: a prospective comparison of external venous catheters and subcutaneous ports. *Am J Ped Hematol Oncol* 1991, **13**, 130–136.
12. Darbyshire PJ, Weightman NC, Speller DCE. Problems associated with indwelling central venous catheters. *Arch Dis Child* 1985, **60**, 129–134.
13. McGovern B, Solenberger R, Reed K. A totally implanted venous access system for long-term chemotherapy in children. *J Ped Surg* 1985, **20**, 725–777.
14. Cairo MS, Spooner S, Sowden L, Bennetts GA, Towne B, Hodder F. Long-term indwelling multipurpose Silastic catheter in pediatric cancer patients treated with aggressive chemotherapy. *J Clin Oncol* 1986, **4**, 784–788.
15. Shulman RJ, Rahman S, Mahoney D, Pokorny WJ, Bloss R. A totally implanted venous access system used in pediatric patients with cancer. *J Clin Oncol* 1987, **5**, 137–140.
16. Conlan MG, Haire WD, Lieberman RP, Lund G, Kessinger A, Armitage JO. Catheter-related thrombosis in patients with refractory lymphoma undergoing autologous stem cell transplantation. *Bone Marrow Transplant* 1991, **7**, 235–240.
17. Braun MA. Image-guided peripheral venous access catheters and implantable ports. *Sem Intervent Med* 1994, **11**, 358–365.
18. Lameris JS, Post PJ, Zonderland HM, Gerritsen PG, Kappers-Klunne MC, Schutte HE. Percutaneous placement of Hickman catheters: comparison of sonographically guided and blinded techniques. *Am J Radiol* 1990, **155**, 1097–1099.
19. McBride KD, Fisher R, Warnock N, Winfield DA, Reed MW, Gaines PA. A comparative analysis of radiological and surgical placement of central venous catheters. *Cardiovasc Intervent Radiol* 1997, **20**, 17–22.
20. Kim FM, Burrows PE, Hoffer FA, Chung T. Interpreting the results of pediatric central venous catheter studies. *Radiographics* 1996, **16**, 747–754.
21. Openshaw KL, Picus D, Hicks ME, Darcey MD, Veseley TM, Picus J. Interventional venous catheters: results and complications in 100 consecutive patients. *J Vasc Intervent Radiol* 1994, **5**, 111–115.
22. Denny DF. The role of the radiologist in long-term central vein access. *Radiology* 1992, **185**, 637–638.
23. Maki D, Ringer M, Alvarado CJ. Prospective randomised trial of povidone iodine, alcohol and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991, **338**, 339–343.
24. Jansen B, Ruiten D, Pulverer G. *In vitro* activity of a catheter loaded with silver and teicoplanin to prevent bacterial and fungal colonization. *J Hosp Infect* 1995, **31**, 238–241.
25. Montecalvo MA, Horowitz H, Gedris C, *et al*. Outbreak of vancomycin, ampicillin and aminoglycoside-resistant *Enterococcus faecum* bacteremia in an adult oncology unit. *Antimicrob Agents Chemother* 1994, **38**, 1363–1367.
26. Hiemenz J, Skelton J, Pizzo PA. Perspective on the management of catheter related infections in cancer patients. *Ped Infect Dis J* 1986, **5**, 6–11.
27. Flynn PM, Shennep JL, Stokes DC, Barrett FF. *In situ* management of confirmed central venous catheter-related bacteremia. *Ped Infect Dis J* 1987, **6**, 729–734.
28. Gray RR. Radiological placement of indwelling central venous lines for dialysis, TPN and chemotherapy. *J Intervent Radiol* 1991, **6**, 133–144.
29. Bagnall HA, Gomperts E, Atkinson JB. Continuous infusion of low-dose urokinase in the treatment of central venous catheter thrombosis in infants and children. *Pediatrics* 1989, **83**, 963–966.
30. Horne MKR, Mayo DJ. Low-dose urokinase infusions to treat fibrinous obstruction of venous access devices in cancer patients. *J Clin Oncol* 1997, **15**, 2709–2714.
31. Mayo DJ, Horne 3rd MK, Summers BL, Pearson DC, Helsabeck CB. The effects of heparin flush on patency of the Groshong catheter: a pilot study. *Oncol Nursing Forum* 1996, **23**, 1401–1405.
32. Smith S, Dawson S, Hennessey R, Andrew M. Maintenance of the patency of indwelling central venous catheters: is heparin necessary? *Am J Ped Hematol Oncol* 1991, **13**, 141–143.
33. Bern MM, Lokich JJ, Wallach SR, *et al*. Very low doses of warfarin can prevent thrombosis in central venous catheters. *Ann Int Med* 1990, **112**, 423–428.
34. Beswetherick H, Baber P. *Wiggly's World*. Trapp A, ed. Victoria Publications, 1993.
35. McCarthy A, Byrne M, Breathnach F, O'Meara A. *In situ* teicoplanin for central venous catheter infection. *Irish J Med Science* 1995, **164**, 125–127.
36. Ley BE, Jalil N, McIntosh J, Smart A, Wilson M, Foot ABM. Bolus or infusion teicoplanin for intravascular catheter associated infections in immunocompromised patients? *J Antimicrob Chemother* 1996, **38**, 1091–1095.
37. Wiener ES, McGuire P, Stolar CJH, *et al*. The CCSG prospective study of venous access devices: an analysis of insertions and causes for removal. *J Ped Surg* 1992, **27**, 155–165.
38. Jones GR, Konsler GK, Dunaway RP, Lacey SR, Azizkhan RG. Prospective analysis of urokinase in the treatment of catheter sepsis in pediatric hematology-oncology patients. *J Ped Surg* 1993, **28**, 350–357.
39. Atkinson JB, Chamberlin K, Boody BA. A prospective randomized trial of urokinase as an adjuvant in the treatment of proven Hickman catheter sepsis. *J Ped Surg* 1998, **33**, 714–716.
40. Breaux CWJ, Duke D, Georgeson KE, Mestre JR. Calcium phosphate crystal occlusion of central venous catheters used for total parenteral nutrition in infants and children: prevention and treatment. *J Ped Surg* 1987, **22**, 829–832.
41. Shulman RJ, Reed T, Pitre D, Laine L. Use of hydrochloric acid to clear obstructed central venous catheters. *JPEN J Parent Ent Nutr* 1988, **12**, 509–510.

42. Werlin SL, Lausten T, Jessen S, *et al*. Treatment of central venous catheter occlusions with ethanol and hydrochloric acid. *JPEN J Parent Ent Nutr* 1995, **19**, 416–418.
43. Harris JL, Maguire D. Developing a protocol to prevent and treat pediatric central venous catheter occlusions. *J Intrav Nursing* 1999, **22**, 194–198.
44. Mauer AM, Burgess JB, Donaldson SS, *et al*. Special nutritional needs of children with malignancies: a review. *JPEN J Parent Ent Nutr* 1990, **14**, 315–324.
45. Orguz A, Karadeniz C, Pelit M, Hassanoglu A. Arm anthropometry in evaluation of malnutrition in children with cancer. *Ped Hematol Oncol* 1999, **16**, 35–41.
46. Coates TD, Rickard KA, Grosfeld JL, Weetman RM. Nutritional support of children with neoplastic diseases. *Surg Clin North Am* 1986, **66**, 1197–1212.
47. Rickard KA, Godshall BJ, Loghmani ES, *et al*. Integration of nutritional support into oncological treatment protocols for high and low nutritional risk children with Wilm's tumor: a prospective randomized study. *Cancer* 1989, **64**, 491–509.
48. van Eys J. Nutrition in the treatment of cancer in children. *J Am Coll Nutr* 1984, **3**, 159–168.
49. van Eys J. The pathophysiology of undernutrition in the child with cancer. *Cancer* 1986, **58**, 1874–1880.
50. Grant MM, Rivera LM. Anorexia, cachexia and dysphagia: the symptom experience. *Sem Oncol Nursing* 1995, **11**, 266–271.
51. Toomey D, Redmond HP, Bouchier-Hayes D. Mechanisms mediating cancer cachexia. *Cancer* 1995, **76**, 2418–2426.
52. Daley SE, Pearson ADJ, Craft AW, *et al*. Whole body protein metabolism in children with cancer. *Arch Dis Child* 1996, **75**, 273–281.
53. Andrassy RJ, Chawals WJ. Nutritional support of the pediatric oncology patient. *Nutr* 1998, **14**, 124–129.
54. den Broeder E, Lippens RJJ, van't Hof MA, Tolboom JM, Sengers RCA, van Staveren WA. Association between the change in nutritional status in response to tube feeding and the occurrence of infections in children with a solid tumour. *Ped Hematol Oncol* 2000, **17**, 567–575.
55. Donaldson SS, Wesley MN, DeWys WD, Suskind RM, Jaffe N, van Eys J. A study of the nutritional status of pediatric cancer patients. *Am J Dis Child* 1981, **135**, 107–112.
56. Weir J, Reilly JJ, McColl JH, Gibson BE. No evidence for an effect of nutritional status at diagnosis on prognosis in children with acute lymphoblastic leukemia. *J Ped Hematol Oncol* 1998, **20**, 534–538.
57. Smith DE, Stevens MCG, Booth IW. Malnutrition at diagnosis of malignancy in childhood: common but mostly missed. *Eur J Ped* 1991, **150**, 318–322.
58. Tyc VL, Vallelunga L, Mahoney S, Smith BF, Mulhern RK. Nutritional and treatment related characteristics of pediatric oncology patients referred or not referred for nutritional support. *Med Ped Oncol* 1995, **25**, 379–388.
59. Warner JT, Cowan FJ, Dunstan FDJ, Gregory JW. The validity of body mass index for the assessment of adiposity in children with disease states. *Ann Hum Biol* 1997, **24**, 209–215.
60. Frisancho AR, Tracer DP. Standards of arm muscle by stature for the assessment of nutritional status of children. *Am J Physic Anthropol* 1987, **73**, 459–465.
61. den Broeder E, Lippens RJJ, van't Hof MA, *et al*. Naso-gastric tube feeding in children with cancer: the effect of two different formulas on weight, body composition, and serum protein concentrations. *JPEN J Parent Ent Nutr* 2000, **24**, 351–360.
62. Merritt RJ, Kalsch M, Davis-Rouix L, Ashley-Mills A, Siegel B. Significance of hypoalbuminemia in pediatric oncology patients — malnutrition or infection. *JPEN J Parent Ent Nutr* 1985, **9**, 303–306.
63. Young VR, Sergio Marchini J, Cortiella J. Assessment of protein nutritional status. *J Nutr* 1990, **11**, 1496–1502.
64. Bowling TE, Silk DBA. Enteral feeding — problems and solutions. *Eur J Clin Nutr* 1994, **48**, 379–385.
65. Pietsch JB, Ford C, Whitlock JA. Nasogastric tube feeding in children with high-risk cancer: a pilot study. *J Ped Hematol Oncol* 1999, **21**, 111–114.
66. Papadopoulou A, MacDonald A, Williams AD, Darbyshire PJ, Booth IW. Enteral nutrition after bone marrow transplantation. *Arch Dis Child* 1997, **77**, 140–143.
67. Copeman MC. Use of total parenteral nutrition in children with cancer: a review and some recommendations. *J Hematol Oncol* 1994, **11**, 463–470.
68. Roy CC, Belli DC. Hepatobiliary complications associated with TPN: an enigma. *J Am Coll Nutr* 1985, **4**, 651–660.
69. Christensen ML, Hanock ML, Gattuso J, *et al*. Parenteral nutrition associated with increased infection rate in children with cancer. *Cancer* 1993, **72**, 2732–2738.
70. Klein S, Koretz RL. Nutrition support in patients with cancer: what do the data really show? *Nutr Clin Practice* 1994, **9**, 91–100.
71. Heubi JE. Whenever possible, use the gut! *J Ped Hematol Oncol* 1999, **21**, 88–91.
72. Bowling TE, Raimundo AH, Grimble GK, Silk DBA. Reversal by short chain fatty acids of colonic fluid secretion induced by enteral feeding. *Lancet* 1994, **342**, 1266–1268.
73. Roediger WEW. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 1980, **21**, 793–798.
74. Klimberg VS, Souba WW, Dolson DJ, *et al*. Prophylactic glutamine protects the intestinal mucosa from radiation injury. *Cancer* 1990, **66**, 62–68.
75. Fox AD, Kripke SA, De Paula J, Berman JM, Settle RG, Rombeau JL. Effect of a glutamine-supplemented enteral diet on methotrexate-induced enterocolitis. *J Parent Ent Nutr* 1988, **12**, 325–331.
76. Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. *Cancer* 1998, **83**, 1433–1439.
77. Fischer JE. Nutritional support of the intensive care unit patient. In Najarian J, Delaney J, eds. *Progress in Trauma and Critical Care*. St Louis, Mosby, 1996, 355–370.
78. Lloyd DA. Central venous catheters for parenteral nutrition: a double-edged sword. *J Ped Surg* 1997, **32**, 943–948.
79. Ziegler TR, Young LS, Benfell K, *et al*. Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomized, double blind controlled study. *Ann Int Med* 1992, **116**, 821–828.
80. Buchman AL. Glutamine: is it a conditionally required nutrient for the human gastrointestinal system? *J Am Coll Nutr* 1996, **15**, 199–205.
81. Jebb SA, Marcus R, Elia M. A pilot study of oral glutamine supplementation in patients receiving bone marrow transplants. *Clin Nutr* 1995, **14**, 162–165.
82. MacBurney M, Young LS, Ziegler TR, Wilmore DW. A cost-evaluation of glutamine-supplemented parenteral nutrition in adult bone marrow transplant patients. *J Am Dietet Assoc* 1994, **94**, 1263–1266.
83. Schloerb PR, Amare M. Total parenteral nutrition with glutamine in bone marrow transplantation and other clinical applications (a randomized, double blind study). *JPEN J Parent Ent Nutr* 1993, **17**, 407–413.