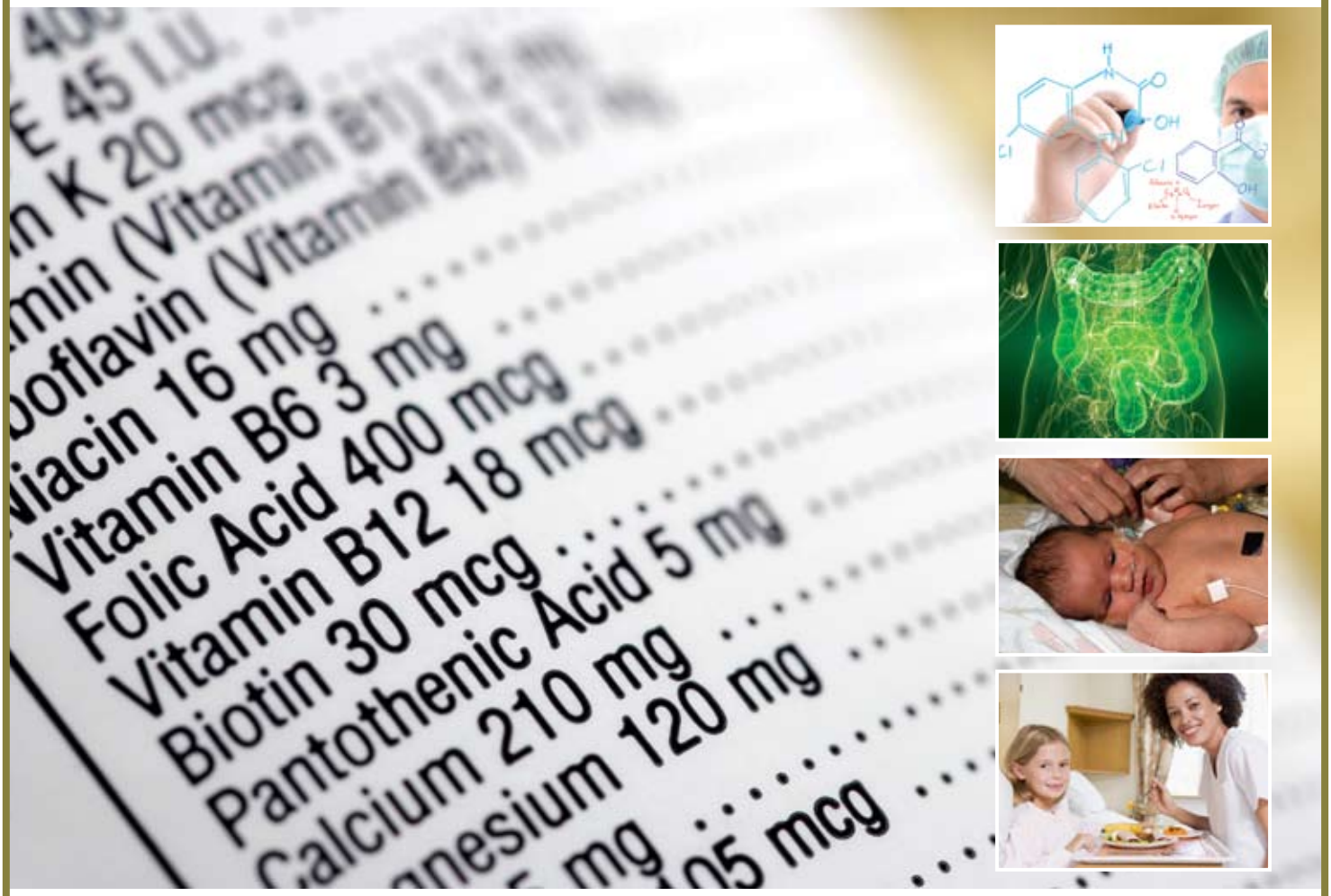
ISSN 003-8-2469

SASPEN

2010 Congress Supplement

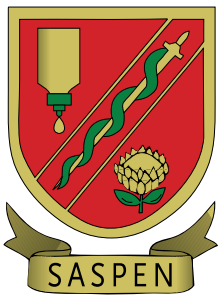


Clinical Nutrition Challenges:
Evidence vs Practice

3-5 March 2010
Spier Estate, Stellenbosch

Supported by an educational grant from:

ISSN 003-8-2469 S Afr J Clin Nutr 2010 volume 23 number 1 Supplement (February)



This supplement has been peer reviewed and is an official supplement to

S Afr J Clin Nutr 2010;23(1): S1-S76

Guest editors

Janicke Visser BSc (Diet), M (Nutr)
Senior Lecturer and Postgraduate Programme Coordinator
Division: Human Nutrition
Faculty of Health Sciences
Stellenbosch University, South Africa

Berna Harmse MSc (Diet)
Private Practitioner
Panorama Medi-Clinic
Cape Town, South Africa

Renée Blaauw PhD (Nutr)
Associate Professor and Deputy Head; Academic
Division of Human Nutrition
Faculty of Health Sciences
Stellenbosch University, South Africa

Demetre Labadarios MBChB, PhD, FACN
Executive Director
Knowledge Systems: Nutrition
Human Sciences Research Council
Cape Town, South Africa

Correspondence to:
Prof Demetre Labadarios, editor@sajcn.co.za

INDEX

CLINICAL NUTRITION CHALLENGES – EVIDENCE VS PRACTICE
SASPEN CONGRESS 2010 ACADEMIC PROGRAMME:

TIME	WEDNESDAY : 3 MARCH 2010	THURSDAY : 4 MARCH 2010	FRIDAY : 5 MARCH 2010	
07:30	Registration			
08:15	Opening and Welcome – *Prof D Labadarios*			
08:30 – 09:00	**Plenary 1** *Chairpersons: D Labadarios, K Mokoena* **Intestinal failure in childhood** *Prof O Goulet* 3	**Plenary 3** *Chairpersons: M Pentz-Kluyts, N Bowley* **Malnutrition – What is it?** *Prof D Labadarios*	**Plenary 5** *Chairpersons: R Blaauw, A Prinsloo* **Micronutrients: Do small things matter?** *Mrs J Visser* 58	
09:00 – 10:30	**Symposium 1** (Sponsored by Adcock Ingram) *Chairpersons: D Labadarios, K Mokoena* **TPN Lipids: Uses and Limitations** 1. Lipid emulsions in parenteral nutrition: does one size fit all? *Prof A Laviano* 8 2. Optimal composition of intravenous lipids *Prof G Kreymann* 11	**Symposium 4** (Sponsored by NNIA) *Chairpersons: M Pentz-Kluyts, N Bowley* **The Gut in Paediatrics – Silent but Powerful** **1. Nutrition in paediatric Crohn's disease** *Prof O Goulet* 33 **2. Nutritional implications of food allergies** *Dr H Steinman* 37 **3. Causes and management of diarrhoea in children in a clinical setting** *Dr ML Cooke* 42	**Group Work and Case Studies discussions - Adults** *Facilitator:* *Prof R Blaauw* *Expert opinion:* *Prof P Dechelotte*	**Group Work and Case Studies discussions - Paediatrics** *Facilitator:* *Mrs A Prinsloo* *Expert opinion:* *Prof O Goulet*
10:30 – 11:00	TEA	TEA	TEA	
11:00 – 12:30	**Symposium 2** (Sponsored by NNIA) *Chairpersons: J Downs, T van der Spuy* **Paediatrics** 1. Diarrhoea and malnutrition *Dr ED Nel* 15 2. Nutrition in children post-transplantation *Dr EA Goddard* 19 3. Management of severe malnutrition *Ms C Schübl* 22	**Oral presentations** *Chairpersons: M Herselman, D Mthuli* 11:00 – 11:15 Agreement between NRS-2002 and MUST nutrition risk scores – a retrospective study *A Dannhauser, M Nel* 71 • 11:15 – 11:30 Agreement between estimated and measured heights and weights in hospitalised patients – a retrospective study *L van den Berg, A Dannhauser, M Nel* 73 • 11:30 – 11:45 The relationship between serum protein and mortality in adults on long-term haemodialysis. A Meta-Analysis *M Herselman, N Esau, JM Kruger, D Labadarios, MR Moosa* 75 • 11:45 – 12:00 Nutritional management of common opportunistic infections *E Mutemi* 76 • 12:00 – 12:30 SASPEN BGM	**Symposium 6** *Chairpersons: D Labadarios, B Harmse* **The Gut in Adults – Silent but Powerful** 1. Nutritional management of gastrointestinal malignancies *Mrs R Smalberger* 62 2. The gastrointestinal tract and HIV pathogenesis *Ms J Downs* 65 3. Gut atrophy: in need of clinical perspective? *Prof D Labadarios*	
12:30 – 13:30	LUNCH	LUNCH	**Plenary 6** *Chairpersons: D Labadarios, B Harmse* **The ethical approach to evidence-based medicine.** *Prof M Kruger* 69	
13:30 – 15:00	**Symposium 3** (Sponsored by Fresenius Kabi) *Chairpersons: R Blaauw, D McDonald* **Conditionally Essential Nutrients** 1. Pharmaconutritional modulation of intestinal protein metabolism *Prof P Dechelotte* 2. The do's and don'ts of arginine supplementation *Dr S Chetty* 25 3. Immunonutrition in ARDS *Dr I Joubert*	**Symposium 5** (Sponsored by Abbott Nutritionals) *Chairpersons: J Visser, C MacDougall* **The worst of all evils? … Glucose** 1. The metabolic syndrome – What is the value of its identification? *Mrs A Till* 47 2. Glucose: the worst of all evils? *Ms A Prins* 50 3. The use of specialised enteral formulae for patients with diabetes mellitus *Prof R Blaauw* 55	CLOSING – *Prof D Labadarios*	
15:00 – 15:30	TEA	TEA		
15:30 – 16:00	**Plenary 2** *Chairpersons: A Prins, L van den Berg* **New developments in clinical practice guidelines** *Prof G Kreymann* 29	**Plenary 4** *Chairpersons: A Dannhauser, G Landau* **Immunonutrition: Where, when and why?** *Prof P Dechelotte*		

Intestinal failure in childhood

Goulet O, MD, PhD
Integrated program of Intestinal Failure, Home Parenteral Nutrition and Liver-Intestinal Transplantation,
National Reference Center for Rare Digestive Diseases, Hôpital Necker – Enfants Malades, Université Paris 5-René Descartes, Paris, France.
Correspondence to: Prof Olivier Goulet, e-mail: olivier.goulet@nck.aphp.fr
Keywords: citrulline; congenital enteropathy; home parenteral nutrition chronic intestinal pseudoobstruction; intestinal failure; intestinal transplantation; liver transplantation; parenteral nutrition; short bowel syndrome

Abstract

Intestinal failure (IF) requires the use of parenteral nutrition (PN) for as long as it persists and in case of irreversible IF may be an indication for intestinal transplantation (ITx). Biological evaluation of IF is becoming possible with the use of plasma citrulline as a marker of intestinal mass. Short bowel syndrome (SBS) is the leading cause of intestinal failure in infants while few epidemiological data are to date available. Data on morbidity and mortality in paediatric patients with SBS are very limited but long-term outcomes seem to be improving. Other causes of intestinal failure include neuro-muscular intestinal disease and congenital disease of enterocyte development. The management of IF should include therapies adapted to each type and stage of IF based on a multidisciplinary approach in centres involving paediatric surgery, paediatric gastroenterology, parenteral nutrition expertise, home-parenteral nutrition programme, liver-intestinal transplantation experience. Timing for referral of patients in specialised centres remains a crucial issue.

S Afr J Clin Nutr 2010;23(1) Supplement:S03-S07

Intestinal failure (IF) results from the critical reduction of functional gut mass below the minimal amount necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for maintenance in adults or growth in children. IF requires parenteral nutrition (PN) for as long as it persists.

Short bowel syndrome (SBS) was one of the first recognised conditions of protracted IF. With the increasing and successful use of long-term PN during the last three decades, several other causes of IF have emerged.

Long-term PN and home-PN are the mainstay of therapy, independent of the nature of "Intestinal failure" (IF) which can be total or partial, permanent or temporary.[1–3] Some patients remain partially or almost fully dependent on PN for years or forever and are thus considered to have permanent IF. Complications of IF and/or PN limiting the use of long-term PN raise the question of intestinal transplantation (ITx).

Assessment of intestinal failure

Citrulline, a non essential amino acid, mostly produced by enterocytes is a biological marker of functional gut mass.[4,5] Studies performed in children with short bowel syndrome also emphasise the value of plasma citrulline as a biomarker of gut mass.[6,7] Whether plasma citrulline levels are predictive of intestinal recovery, or not, remains to be confirmed. One of the best indicators for predicting full recovery of intestinal function remains the growth of the child as reflected in normal weight gain and growth velocity for age when fully, orally and/or enterally, fed.

Causes of intestinal failure

Short bowel syndrome

The incidence of SBS is difficult to establish, ranging between 2 and 5 per million live births.[8] The causes of SBS differ significantly between series (Table I).[8–11] Necrotising enterocolitis (NEC) remains the leading cause of SBS especially in premature infants. The percentage of SBS caused by NEC ranges from 14 to 43% depending on the country that data originate from.[9–13] Several studies included in a meta-analysis have shown that probiotics administration might be helpful in decreasing incidence of NEC in preterm infants.[14] Other causes of short bowel syndrome include resection following intestinal atresia, gastroschisis, other congenital malformation including midgut volvulus from malrotation, and radiation enteritis. Crohn's disease should no longer be a cause of SBS resulting from repeated small bowel resection.

Survival of SBS infants has increased during the last decades. More than 80 % of infants and children now survive after extensive small bowel resection in the neonatal period.[9,15] Prognosis is related to age adjusted intestinal length, ileocaecal valve (ICV), colon preservation and occurrence of cholestasis. In SBS patients most of the deaths are caused by liver failure or sepsis and occur within one year post-event. A survey including 87 children who had undergone extensive neonatal SB resection, were followed up over a mean 15 year-period.[9] The overall survival was 89.7% depending on the year of birth. By multivariate analysis, PN duration was significantly influenced by the length of residual intestine and the absence of ileocaecal valve. After PN weaning, they grow up normally with normal puberty and final height as expected from genetic target height.

Nutritional support: In order to maintain an optimal nutritional status with normal growth and development oral feeding skills have to be acquired and maintained. PN is the corner stone of management but as much nutrition as possible should be provided to the patient via the enteral route in order to improve the physiological processes of intestinal adaptation. Oral feeding, which is known to enhance GI secretions, salivary Epidermal Growth Factor (EGF) release and gallbladder motility, is recommended. In addition, oral feeding by promoting gut motility improves intestinal bacterial clearance thus reducing the risk of small intestinal bacterial overgrowth.[16] However the mode of administration of feeding varies among different practitioners regarding the composition of the enteral feed (elemental, semi-elemental or polymeric) and mode of delivery (gastric tube feeding or oral feeding).[17] Moreover current studies do not provide evidence based recommendations for using special diets such as amino acid based enteral formulae. Long term follow up of growth after PN weaning is mandatory in order to decide on the need to restart nutritional support, when required. [9]

Rehabilitation therapies for short bowel patients

Intestinal flora related disorders

The colon is a crucial partner for small intestinal adaptation and function in patients who underwent extensive small intestinal resection.[18]

However, colonic hypermetabolism may be responsible for D-lactic acidosis resulting from fermentation of dietary carbohydrate by luminal bacteria in the small bowel. D-lactic acidosis may be associated with clinical symptoms and failure to thrive.[19]

Small bowel bacterial overgrowth (SBBO) is a frequent complication that is likely to occur in the case of ICV resection, poor motility of a dilated small bowel segment, or when a tight anastomosis is present. SBBO is mostly responsible for mucosal inflammation, which may further exacerbate nutrient malabsorption and protein sensitisation, deconjugate bile salts and deplete bile salt pool with subsequent impaired micellar solubilisation resulting in steatorrhea and fat soluble vitamins malabsorption. SBBO increases the risk of intestinal bacterial translocation which increases the risk for liver disease.[20,21]

Antibiotic therapy should be used very cautiously and with due attention to their effects on the colonic bacterial microflora which should be preserved for production of short chain fatty acids. The use of probiotics might be helpful but it is not yet been adequately documented in SBS paediatric patients.[22]

Non-transplant surgery: Surgical procedures have been proposed for increasing nutrient and fluid absorption by either slowing the transit or increasing surface area. Such procedures include intestinal valves, reversed intestinal segments, colon interposition, but have all yielded conflicting results.[23]

In selected patients with dilated bowel segments, longitudinal intestinal lengthening and tailoring (LILT) have been extensively performed.[24] LILT has the theoretical benefit of not only tapering the dilated segment but also of using the divided intestine to increase total small bowel length. The anatomical criteria that have been suggested for patient selection for this procedure include (i) intestinal diameter (> 3 cm); (ii) length of residual small bowel (> 40 cm); and (iii) length of dilated bowel (> 20 cm). This procedure allows improvement in more than 50% of patients in terms of intestinal transit time, stool frequency, intestinal absorption rate, weight gain and PN weaning.[25] LILI is not yet recommended for patients with severe liver disease or cirrhosis.

Serial transverse enteroplasty (STEP) has also been reported for use in infants and children with SBS.[26] Indications for the procedure have broadened STEP's use beyond the scope of SBS to include bacterial overgrowth and neonatal intestinal obstruction with dilated proximal intestine. The first 38 patients enrolled in the International STEP Data Registry were reviewed.[27] More data are requires to establish the long term safety and efficacy of the procedure, with the goal of improving patient selection criteria and optimal time of surgical intervention.

Trophic factors

The use of recombinant human growth hormone (rhGH) is associated with conflicting results in adult patients with SBS who were included in both, open and/or randomised clinical trials.[28,29] Few such studies have been reported in children with SBS.[30,31]

Glucagon-like peptide-2 (GLP-2) has been reported to improve intestinal absorption and nutritional status in SBS patients with impaired postprandial GLP-2 secretion in whom the terminal ileum and the colon had been resected.[32] The results of a paediatric study suggest that in infants with intestinal dysfunction, GLP-2 levels are correlated with residual small bowel length and nutrient absorption, and may be predictive of outcome[33] GLP-2 might be the most logical medical approach for early management of SBS patients especially those with ileal resection. To date, there are no published studies involving infants or children.

Epidermal growth factor (EGF) has also been shown to have a role both in maintaining epithelial tissues as well as controlling intestinal adaptation.[34] Five SBS paediatric patients (< 25% bowel length predicted for age) were treated with human recombinant EGF.[35] However, this study does not allow drawing any conclusion.

Insulin influences intestinal structure and absorptive function.[36] The favourable effect of insulin is relevant and might be considered in patients on PN receiving high intravenous glucose rate that induce insulin release and relative hyperinsulinism. Interestingly, oral insulin has been shown to enhance intestinal adaptation following massive resection in a rat model.[37]

Intestinal neuromuscular diseases

Total colonic aganglionosis (TIA) with jejuno-ileal involvement

This condition is a rare form of Hirschsprung disease (HD). The aganglionosis may extend to encompass the entire colon (total colonic aganglionosis) or very rarely affect the entire intestine (TIA). When the normal ganglionic small bowel is shorter than 50 cm, the probability for permanent PN dependency is high. There is no surgical procedure that can improve intestinal absorption without the colon. Thus, TIA with jejuno-ileal involvement is equivalent to short bowel syndrome without colon. Small bowel transplantation is the ultimate cure. Several patients with a length of normal bowel segment ranging from 15 to 50 cm have been transplanted.[38]

Chronic intestinal pseudo-obstruction syndrome (CIPOS)

This is a very heterogeneous condition in terms of clinical presentation, histopathological features, severity of motility disorders and outcome.[39] Patients with the most severe form of CIPOS, whether myopathic or neuropathic with or without urinary tract involvement, are very uncomfortable because of the association of enterostoma, gastrostomy tube, central line and sometimes vesicostomy. ITx becomes logical, but difficult, because of the requirement of multiple previous surgical procedures and associated disorders such as uropathy or peripheral neuropathy.[40]

Congenital enteropathy

Microvillous atrophy (MVA)

Among the causes of intractable diarrhoea of early infancy,[41] MVA is a congenital constitutive intestinal epithelial cell disorder leading, in its typical early-onset form, to PIF. MVA is characterised by a lack of microvilli on the surface of enterocytes and the occurrence of intracellular vacuolar structures containing microvilli, Microvillous Inclusion Disease (MVID).[42] Following homozygosity mapping in a single kindred with MVID, nonsense and missense mutations in MYO5B, encoding type Vb myosin motor protein were identified. In addition, mislocalisation of transferrin receptor in MVID enterocytes suggests that MYO5B deficiency causes defective trafficking of apical and basolateral proteins in MVID.[43]

The largest multi-centre survey of 23 MVA patients[44] revealed an extremely reduced life expectancy with a one-year survival rate of less than 25%. Most children died of septic complications, liver failure or metabolic decompensation. Management is based on PN since all others medical approaches have failed. Complications related to inadequate PN do limit long-term survival. Finally, even with adequate long-term PN and normal growth, most children continue to manifest high and disabling levels of stool output that results in a high risk for severe dehydration and requires daily fluid and electrolyte replacement . Thus, ITx has become the only definitive treatment for this rare intestinal disease. ITx usually involves isolated intestine or intestine combined with the liver and colon.[45]

Intestinal epithelial dysplasia (IED) or tufting enteropathy

Congenital tufting enteropathy (CTE) is a rare autosomal recessive diarrhoeal disorder presenting in the neonatal period. CTE is characterised by intestinal epithelial cell dysplasia leading to severe malabsorption and significant morbidity and mortality.[46,47] The pathogenesis and genetics of this disorder are not well understood. Mutations in the gene for EpCAM are responsible for CTE.[48] Several cases of CTE have been reported as being associated with phenotypic abnormalities such as choanal atresia, rectal atresia, esophageal atresia and a non-specific punctiform keratitis involving about 60% of patients.

This cause of neonatal diarrhoea requires permanent PN. However, it would appear that some infants have a rather milder phenotype than others. Because of the preservation of some degree of intestinal function and a more limited volume of stool output, some patients need only partial long-term PN. Even in such cases, careful monitoring should be implemented in order to avoid progressive growth retardation. In most patients, the severity of intestinal malabsorption and diarrhoea, hoever, make such patients totally dependent on long-term PN with its attendant complications. In such patients intestinal transplantation may, thus, become an indication.

Autoimmune enteropathy (AIE) causes severe IF.[49] Mutations in the *FOXP3* gene cause AIE.[50] Non-functional *FOXP3* leads to a tremendous hyperactivation of T cells, resulting in autoimmune aggression, such as seen in patients with immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked (IPEX) syndrome, a subgroup of AIE. The use of T-cell immunosuppressive drugs, such as tacrolimus or rapamycine following steroids treatment, seems to be beneficial in some patients. However, long-term remission is not always possible.[51] Bone marrow transplantation might be the treatment of choice in those patients who do not respond to immunosuppression.[52,53]

From intestinal failure to intestinal transplantation

PN and home-PN remain the mainstay of therapy, independent of the nature of IF which can be total or partial, permanent or temporary.[2,3,54] However, some patients develop complications while receiving daily long-term PN for IF. These patients can be considered as candidates for intestinal transplantation.

Intestinal failure-related liver disease

Cholestasis and liver fibrosis are associated with impaired intestinal function, disruption of enterohepatic cycle (ileal disease or resection), intestinal stasis with subsequent intra-luminal bacterial overgrowth and/or translocation (endotoxinemia), recurrent catheter related sepsis, while prematurity itself might be an associated factor aggravated by inadequate PN.[3] Preventing or reversing liver disease is possible by stimulating the enterobiliary axis by early oral/enteral feeding, by reducing intra-luminal bacterial overgrowth, by using ursodesoxycholic acid, by preventing catheter related sepsis, and by providing adapted PN with appropriate amino acids solutions, lipid emulsions, micronutrients provison and cyclic infusion.[3] The guidelines on PN provide extensive recommendations for adapting nutritional support.[54]

Some SBS children with a length of remnant intestine theoretically sufficient to achieve PN weaning, liver disease interferes with gut adaptation and can lead to early death. The small size and poor condition of these infants means they are poor candidates for combined liver-intestine Tx, while many of them die before a combined graft is available. Case reports or small samples of isolated liver transplantation (ILTx) in SBS paediatric patients have been reported.[55] Prevention of NEC, screening for high risk patients such as gastroschisis or NEC and prevention of IF related liver disease might improve outcome for such patients and decrease the need for any type of liver grafting alone or in combination with small intestine.[3,56]

Indications for Intestinal Transplantation

Some patients may remain partially or almost fully dependent on PN for years or forever and are thus considered to have permanent IF. Moreover, patients who develop complications while receiving daily long-term PN for IF are candidate for ITx. A European survey[57] studied the candidacy of home-PN patients for ITx and timing for referral for ITx. Candidacy was assessed by the USA Medicare and American Transplantation Society criteria,[58,59] categorised as:

(i) life-threatening home parenteral nutrition (HPN) complications;

(ii) high risk of death due to the gastrointestinal disease; and

(iii) IF with high morbidity or patient HPN refusal.

On the basis of these criteria, physicians judged candidacy for ITx as immediate or potential. The main indications for HPN were SBS (52%), chronic intestinal pseudoobstruction syndrome (CIPOS) (25%) and congenital mucosal disease (14.5%). Candidacy was considered for 57 patients (34.3%) with the following underlying disease: congenital enteropathy (26.3%), CIPOS (26.3%), SBS (19.3%). Immediate candidacy was judged for 15.8% of paediatric candidates (i.e < 50% of candidates because of HPN-related liver failure).

The irreversibility of SBS related IF has to be demonstrated before any ITx can be considered. IF may be clearly and early considered as *irreversible* in patients with duodenocolic anastomosis after extensive intestinal resection for midgut volvulus or children with total aganglionosis with small bowel length less than 50 cm and infants suffering congenital enteropathy such as MVID or IED. All these patients are potential candidates for ITx. Since these patients will remain indefinitely dependent on PN, they must be referred early for transplantation on good nutrional status and with the minimal possible IF and PN related complications. Severe liver disease should no longer be considered as an indication for ITx. In contrast, it can be rather difficult to confirm irreversibility of IF in SBS or CIPOS patients for which all medical and/or surgical approaches have to be tried before any decision of ITx can be taken.[3] In these particular cases, if long-term PN is effective and well-tolerated, it can be used for a prolonged period of time without ITx. Finally, few patients require immediate transplantation for life threatening conditions.[57]

Extensive multidisciplinary discussion involving transplant surgeons, paediatric gastroenterologists, specialised nurses, dieticians, social workers and psychologists is mandatory before any decision is taken for a specific child. Assessment and decisions should be based on the occurrence of the complications listed in the position paper of the American Society of Transplantation.[60]

Type of intestinal transplantation

Children with severe advanced and progressive hepatic fibrosis are usually listed for LITx. However, some PN-dependent patients with advanced liver dysfunction may experience functional and biochemical liver recovery which appears to parallel autologous gut salvage.[61,62]

Factors impacting adversely on the survival of children with intestinal failure referred for ITx include : age below one year, multiple prior surgery, bridging fibrosis or cirrhosis, bilirubin levels over 3 mg/dl, and thrombocytopaenia.[63] The United Network for Organ Sharing (UNOS) report indicates that mortality on the ITx waiting list is higher than on any other transplant waiting list.[64] The ITx Registry confirmed that transplantations performed in patients waiting at home *versus* waiting in hospital have a better than one-year survival (74% versus 59%; $P < 0.00001$).[65] The trend to transplant proportionately more patients who are waiting at home was a major factor contributing to the recently improved graft and patient survival rates.[65] Indeed, it is well established that patients with end stage liver disease are at risk of dying before transplantation and are also at higher risk of post-operative complications and death.[63,64] We recently reported factors impacting on survival after Tx.[66] Such factors should also be considered before listing a patient for ITx.

Intestinal failure rehabilitation centre

Long-term management of IF has become a very important goal. Few centres manage all the stages of IF from onset to ITx, including home PN programmes.[2,67] SBS remains the most common indication for ITx accounting for 63% of case *versus* 32% of other indications in our transplantation centre.[65,66] Liver complications of poor functioning remnant small intestine with intestinal stasis and subsequent sepsis from bacterial overgrowth may be prevented by appropriate medico-surgical approaches. In addition to the prevention of complications, global management should also aim to demonstrate the irreversibility of IF in spite of all medico-surgical attempts at digestive autonomy.[3]

The development of integrated centres involved in all stage of IF management should be encouraged. Such centres should have a high level of expertise in the fields of paediatric Gastroenterology and Clinical Nutrition with a well organised Home-PN programme, together with experienced paediatric surgeons involved in SBS-non-transplant surgery as well as in intestinal transplantation.[67,68] ITx offers not only an improved quality of life but also maintains optimal nutritional status.[69,70]

Table I: Main causes of short bowel syndrome

	International[8]	France[9]	Canada[10]	USA[11]
Intestinal atresia	23%	39%	30%	30%
Volvulus	24%	24%	10%	10%
Gastroschisis	14%	14%	12.5%	17%
NEC	27%	14%	35%	43%

References

1. Goulet O, Sauvat F. Short bowel syndrome and intestinal transplantation in children. Curr Opin Clin Nutr Metab Care. 2006;9:304–13.
2. Colomb V, Dabbas-Tyan M, Taupin P, Talbotec C, Révillon Y, Jan D, De Potter S, Gorski-Colin AM, Lamor M, Herreman K, Corriol O, Landais P, Ricour C, Goulet O.Long-term outcome of children receiving home parenteral nutrition: a 20-year single-centre experience in 302 patients. J Pediatr Gastroenterol Nutr. 2007;44:347–53.
3. Goulet O, Ruemmele F. Causes and management of intestinal failure. Gastroenterology 2006;130:516–528.
4. Crenn P, Vahedi K, Lavergne-Slove A, Cynober L, Matuchansky C, Messing B. Plasma citrulline: A marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology. 2003;124:1210–9.
5. David AI, Gaynor JJ, Zis PP, Conanan L, Goldsmith L, Esquenazi V, Selvaggi G, Weppler D, Nishida S, Moon J, Madariaga JR, Ruiz P, Kato T, Levi DM, Kleiner G, Tryphonopoulos P, Tzakis AG. An association of lower serum citrulline levels within 30 days of acute rejection in patients following small intestine transplantation. Transplant Proc. 2006;38:1731–2.
6. Jianfeng G, Weiming Z, Ning L, Fangnan L, Li T, Nan L, Jieshou L. Serum citrulline is a simple quantitative marker for small intestinal enterocytes mass and absorption function in short bowel patients. J Surg Res. 2005;127:177–82.
7. Bailly-Botuha C, Colomb V, Thioulouse E, Berthe MC, Garcette K, Dubern B, Goulet O, Couderc R, Girardet JP. Plasma citrulline concentration reflects enterocyte mass in children with short bowel syndrome. Pediatr Res. 2009;65:559–63.
8. Koffeman GI, van Gemert WG, George EK, Veenendaal RA. Classification, epidemiology and aetiology. Best Pract Res Clin Gastroenterol. 2003;17:879–93.
9. Goulet O, Baglin-Gobet S, Talbotec C, Fourcade L, Colomb V, Sauvat F, Jais JP, Michel JL, Jan D, Ricour C.Outcome and long-term growth after extensive small bowel resection in the neonatal period: a survey of 87 children. Eur J Pediatr Surg 2005;15:95–101.
10. Wales PW, de Silva N, Kim JH, Lecce L, Sandhu A, Moore AM. Neonatal short bowel syndrome: a cohort study. J Pediatr Surg 2005;40:755–762.
11. Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, Dicanzio J, Richardson DS, Collier SB, Lo C, Duggan C. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr. 2001;139:27–33.
12. Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N, Vargas JH. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr. 2004;145:157–63.
13. Diamond IR, de Silva N, Pencharz PB, Kim JH, Wales PW. Group for the Improvement of Intestinal Function and Treatment. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. J Pediatr Surg. 2007;42:806–11.

14. Deshpande G, Rao S, Patole S. Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials. Lancet. 2007;369:1614–20.
15. Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, Kuzma-O'Reilly B, Teitelbaum DH. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005;242:403–9; discussion 409–12.
16. Husebye E. The patterns of small bowel motility: physiology and implications in organic disease and functional disorders. Neurogastroenterol Motil. 1999;11:141–61.
17. Jackson CS, Buchman AL. The nutritional management of short bowel syndrome. Nutr Clin Care. 2004;7:114–21.
18. Goulet O, Colomb-Jung V, Joly F. Role of the colon in short bowel syndrome and intestinal transplantation. J Pediatr Gastroenterol Nutr. 2009;48 Suppl 2:S66–71.
19. Puwanant M, Mo-Suwan L, Patrapinyokul S. Recurrent D-lactic acidosis in a child with short bowel syndrome. Asia Pac J Clin Nutr. 2005;14:195–8.
20. Kaufman SS, Loseke CA, Lupo JV et al. Influence of bacterial overgrowth and intestinal inflammation on duration of PN in children with short bowel syndrome. J Pediatr 1997:131:356–361.
21. Forchielli ML, Walker WA. Nutritional factors contributing to the development of cholestasis during total parenteral nutrition. Dev Pediatr. 2003;50:245–67.
22. Matarese LE, Seidner DL, Steiger E. The role of probiotics in gastrointestinal disease. Nutr Clin Pract. 2003;18:507–16
23. Wales PW. Surgical therapy for short bowel syndrome. Pediatr Surg Int. 2004;20:647–57.
24. Bianchi A. Longitudinal intestinal lengthening and tailoring: results in 20 children. J R Soc Med 1997;90:429–32.
25. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 2. Am J Gastroenterol. 2004;99:1823–32.
26. Javid PJ, Kim HB, Duggan CP, Jaksic T. Serial transverse enteroplasty is associated with successful short-term outcomes in infants with short bowel syndrome. J Pediatr Surg. 2005;40:1019–23; discussion1023–4.
27. Modi BP, Javid PJ, Jaksic T, Piper H, Langer M, Duggan C, Kamin D, Kim HB; International STEP Data Registry. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. J Am Coll Surg. 2007;204:365–71.
28. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home PN-dependent short bowel patients: a positive study. Gastroenterology 2003;124:293–302.
29. Parekh NR, Steiger E. Criteria for the use of recombinant human growth hormone in short bowel syndrome. Nutr Clin Pract. 2005;20:503–8.
30. Dabbas-Tyan M, Colomb V, Rosilio M, Landais P, Ricour C, Goulet O. Evaluation of the effect of recombinant human growth hormone (rhGH) treatment of children with short bowel syndrome. J Pediatr Gastroenterol Nutr 2000;31:5165–5166
31. Lifschitz C, Duggan C, Lazngston C, Vanderhoof J, Shulman RJ. Growth Hormone (GH) therapy in children with short bowel syndrome (SBS): a randomized, placebo controlled study. Digestive Disease Week; Orlando 2003:A100.
32. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, Gregory J, Tappenden KA, Holst J, Mortensen PB. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut. 2005;54:1224–31.
33. Sigalet DL, Martin G, Meddings J, Hartman B, Holst JJ. GLP-2 levels in infants with intestinal dysfunction. Pediatr Res. 2004;56:371–6.
34. Iskit SH, Tugtepe H, Ayyildiz SH, Kotiloglu E, Dagli TE, Yegen BC. Epidermal growth factor and bombesin act synergistically to support intestinal adaptation in rats with massive small bowel resection. Pediatr Surg Int. 2005;21:436–40.
35. Sigalet DL, Martin GR, Butzner JD, Buret A, Meddings JB. A pilot study of the use of epidermal growth factor in pediatric short bowel syndrome. J Pediatr Surg. 2005;40:763–8
36. Sukhotnik I, Mogilner J, Shamir R, Shehadeh N, Bejar J, Hirsh M, Coran AG. Effect of subcutaneous insulin on intestinal adaptation in a rat model of short bowel syndrome.Pediatr Surg Int. 2005;21:132–7.
37. Sukhotnik I, Shehadeh N, Shamir R, Bejar J, Bernshten A, Mogilner JG. Oral enhances intestinal re-growth following massive resection in rat. Dig Dis Sci. 2005;50:2379–85.
38. Sauvat F, Grimaldi C, Lacaille F, Ruemmele F, Dupic L, Bourdaud N, Fusaro F, Colomb V, Jan D, Cezard JP, Aigrain Y, Revillon Y, Goulet O. Intestinal transplantation for total intestinal aganglionosis: a series of 12 consecutive children. J Pediatr Surg. 2008 ;43:1833–8.
39. Faure C, Goulet O, Ategbo S, Breton A, Tounian P, Ginies JL, et al. Chronic intestinal pseudoobstruction syndrome: clinical analysis, outcome and prognosis in 105 children. Dig Dis Scie 1999;44:953–959.
40. Loinaz C, Mittal N, Kato T, Miller B, Rodriguez M, Tzakis A. Multivisceral transplantation for pediatric intestinal pseudo-obstruction: single center's experience of 16 cases. Transplant Proc. 2004;36:312–3.
41. Goulet O, Brousse N, Canioni D, et al Syndrome of intractable diarrhoea with persistent villous atrophy in early childhood : A clinicopatological survey of 47 cases. J Pediatr Gastroenterol Nutr 1998;26:151–161.
42. Ruemmele FM, Schmitz J, Goulet O. Microvillous inclusion disease (microvillous atrophy).Orphanet J Rare Dis. 2006;26:1:22.
43. Müller T, Hess MW, Schiefermeier N, et al. MYO5B mutations cause microvillus inclusion disease and disrupt epithelial cell polarity. Nat Genet. 2008;40:1163–5.
44. Goulet O, Sauvat F, Ruemmele F, Caldari D, Damotte D, Cezard JP, Lacaille F, Canioni D, Hugot JP, Berebi D, Sarnacki S, Colomb V, Jan D, Aigrain Y, Revillon Y. Results of the Paris program: ten years of pediatric intestinal transplantation. Transplant Proc 2005;37:1667–70.
45. Ruemmele F, Jan D, Lacaile F, Cezard JP, Canioni D, Phillips AD, Peuchmaur M, Aigrain Y, Brousse N, Schmitz J, Revillon Y, Goulet O. New perspectives for children with microvillous inclusion disease: early small bowel transplantation. Transplantation. 2004;77:1024–8.
46. Goulet O, Kedinger M, Brousse N, Cuenod B, Colomb V, Patey N, de Potter S, Mougenot JF, Canioni D, Cerf-Bensussan N. Intractable diarrhea of infancy: a new entity with epithelial and basement membrane abnormalities. J Pediatr 1995;127:212–9.
47. Goulet O, Salomon J, Ruemmele F, Patey-Mariaud de Serres N, Brousse N. Intestinal epithelial dysplasia (Tufting enteropathy). Orphanet J Rare Dis. 2007 20;2(1):20.
48. Sivagnanam M, Schaible T, Szigeti R, et al. Further evidence for EpCAM as the gene for congenital tufting enteropathy. Am J Med Genet A. 2010;152:222–4.
49. Ruemmele FM, Moes N, de Serre NP, Rieux-Laucat F, Goulet O.Clinical and molecular aspects of autoimmune enteropathy and immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked syndrome. Curr Opin Gastroenterol. 2008;24:742–8. .
50. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome. J Med Genet 2002;39:537–45.
51. Bindl L, Torgerson T, Perroni L, Youssef N, Ochs HD, Goulet O, Ruemmele FM. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr. 2005;147:256–9.
52. Baud O, Goulet O, Canioni D, Le Deist F, Radford I, Rieu D, Dupuis-Girod S, Cerf-Bensussan N, Cavazzana-Calvo M, Brousse N, Fischer A, Casanova JL.Treatment of the immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. N Engl J Med 2001;344:1758–62.
53. Torgerson TR, Linane A, Moes N, Anover S, Mateo V, Rieux-Laucat F, Hermine O, Vijay S, Gambineri E, Cerf-Bensussan N, Fischer A, Ochs HD, Goulet O, Ruemmele FM. Severe food allergy as a variant of IPEX syndrome caused by a deletion in a noncoding region of the FOXP3 gene.. Gastroenterology. 2007;132:1705–17.
54. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R; for the Parenteral Nutrition Guidelines Working Group. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41:S1–S4.
55. Botha JF, Grant WJ, Torres C, Iverson AK, Sudan DL, Shaw BW Jr, Langnas AN. Isolated liver transplantation in infants with end-stage liver disease due to short bowel syndrome.Liver Transpl. 2006;12:1062–6.
56. Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V. Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. J Pediatr Gastroenterol Nutr. 2007;44:459–63.
57. Pironi L, Hébuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V, et al. .Candidates for intestinal transplantation: a multicenter survey in Europe. Am J Gastroenterol 2006;101:1633–43.
58. American Gastroenterological Association medical position statement. short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124:115–1110
59. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003;124:1111–34.
60. Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN, McDiarmid SV, Mittal N, Reyes J, Tzakis AG; American Society of Transplantation. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transpl 2001;5:80–87.
61. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term PN in children. J Parenter Enteral Nutr. 2000;24:345–50.
62. Goulet O, Joly F, Corriol O, Colomb-Jung V Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant. 2009;14:256–61.
63. Bueno J, Ohwada S, Kocoshis S, Mazariegos GV, Dvorchik I, Sigurdsson L, Di Lorenzo C, Abu-Elmagd K, Reyes J.Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg 1999;34:27–33.
64. Fryer J, Pellar S, Ormond D, Koffron A, Abecassis M. Mortality in candidates waiting for combined liver-intestine transplants exceeds that for other candidates waiting for liver transplants. Liver Transpl. 2003;9:748–53.
65. Grant D, Abu-Elmagd K, Reyes J, Tzakis A, Langnas A, Fishbein T, Goulet O, Farmer D on the behalf of the Intestine Transplant Registry. 2003 report of the Intestine Transplant Registry: a new era has dawned. Ann Surg. 2005;241:607–13.
66. Sauvat F, Dupic L, Caldari D, Lesage F, Cézard JP, Lacaille F et al . Factors influencing outcome after intestinal transplantation in children. Transplant Proc. 2006;38:1689–91.
67. Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006 15;24:1231–40.
68. Nucci A, Cartland Burns R, Armah T, Lowery K, Yaworski JA, Strohm S, Bond G, Mazariegos G, Squires R.. Interdisciplinary Management of Pediatric Intestinal Failure: A 10-Year Review of Rehabilitation and Transplantation. J Gastrointest Surg. 2008;12:429–436.
69. Sudan D. Cost and quality of life after intestinal transplantation. Gastroenterology. 2006;130:S132–7.
70. Lacaille F, Vass N, Sauvat F, Canioni D, Colomb V, Talbotec C, De Serre NP, Salomon J, Hugot JP, Cézard JP, Révillon Y, Ruemmele FM, Goulet O. Long-term outcome, growth and digestive function in children 2 to 18 years after intestinal transplantation. Gut. 2008;57:455–61.

Lipid emulsions in parenteral nutrition: does one size fits all?

Laviano A, Rossi Fanelli F
Department of Clinical Medicine, Sapienza University, Rome, Italy
Correspondence to: Alessandro Laviano, e-mail: alessandro.laviano@uniroma1.it
Keywords: lipid emulsions; metabolism; parenteral nutrition; immune response; inflammation

Abstract

Dietary lipids significantly contribute to preserve the efficiency of human metabolism and restore it during disease. Therefore, in the absence of absolute contraindications, it would not appear reasonable to exclude lipid emulsions when prescribing parenteral nutrition (PN). The metabolic role of lipids has been elucidated, and is far more complex than a mere energy-dense source. Indeed, it is now clear that fatty acids impact differently on the inflammatory and immune responses, either promoting or blunting them. Omega-6 fatty acids are the substrate for the production of potent mediators of inflammation, whereas omega-3 fatty acids promote the synthesis of less active factors. Omega-9 fatty acids exert a more neutral impact on immune and inflammatory responses. These specific metabolic activities should therefore be considered when prescribing lipid emulsions in PN. Ideally, the metabolic profile of patients should guide the prescription of lipid emulsions in order to promote the inflammatory response or blunt it according to the clinical needs. This new approach would wholly exploit the metabolic activities of lipid emulsions by providing patients not only with an energy-dense source, but also by priming and/or modulating the immune and inflammatory responses in order to favour healing.

S Afr J Clin Nutr 2010;23(1) Supplement:S08-S10

Lipids are essential components of a healthy diet. This is not simply because some fatty acids cannot be synthesised by human cells and need to be supplied by the diet to prevent clinically relevant deficiencies.[1] Lipids also represent an energy-dense source, and their hydrophobic properties are also critical for the metabolic efficiency of body composition. In the latter regard, cell membranes are largely made by lipids, which are important in maintaining compartamentalisation and cellular integrity. Lipids are also metabolically active, since they serve as the skeleton upon which many hormones are synthesised and influence human metabolism per se. Finally, lipids are thought to have also contributed to the evolution of the human race by serving as a metabolic signal during periods of food availability, thereby triggering the onset of a metabolic milieu favouring energy intake and storage of excess energy as fat depots.[2] Therefore, it should not be surprising that the inclusion of lipid emulsions is recommended when providing PN to patients unable to meet their protein and energy needs via the oral and enteral route.[3] Indeed, if we consider artificial nutrition as a tool to replace oral diet when the latter is not feasible, it seems unreasonable to exclude lipids and the question arises as to whether we adopt that approach when advising a patient who could eat. Nevertheless, lipid emulsions are frequently not considered when prescribing PN and the practice may be related to to concerns regarding their potential toxicity, although it is now clear that their use according to the existing guidelines provides more benefits than harm.

Metabolic effects of lipid emulsions

One gram of lipids provides approximately 9 Kcal. In this regard, lipid emulsions represent an efficient energy source, and contribute to reduce the potential toxicity associated with glucose-based PN and hyperglycaemia.[1,4,5] Lipids are also known to directly influence the inflammatory and immune responses. This effect is mostly related to the specific biochemical structure of fatty acids, and therefore it may vary according to the different composition of lipid emulsions used in PN. It is important to note that commercially available lipid emulsions differ in their fatty acid compositions, and may exert different modulations of inflammatory and immune responses. Therefore, they should be prescribed according to the metabolic profile of the patient, in order to accelerate healing and recovery.

Fatty acids are classified according different classes. The omega nomenclature classifies unsaturated fatty acids according to the distance, in carbon atoms, of the first double bond from the omega end of the carbon chain. The first double bond in position 3 characterises omega-3 fatty acids (i.e. α-linolenic acid). Omega-6 fatty acids (i.e. linoleic acid) have the first double bond 6 carbons from the omega end. Omega-9 fatty acids (i.e. oleic acid) are characterised by the first double bond being in position 9. Although apparently minimally relevant, the position of the double bond significantly influences the metabolic effects of lipids.

The most relevant omega-3 fatty acids in clinical nutrition are polyunsaturated fatty acids found in plants (i.e. α-linolenic acid)

and fish oil [i.e. eicosapentaenoic acid (EPA), docosahexanoic acid (DHA)]. Omega-6 fatty acids are the characterising polyunsaturated fatty acids found in soybean oil (i.e. linoleic acid) and in fats of animal origin. Oleic acid is a monounsaturated fatty acid, which is the primary omega-9 fatty acid found in olive oil.

Oxidative stress

The possibility to fully oxidise glucose via aerobic glycolysis represents one of the major steps contributing to the evolution of species from primordial cells into multicellular organisms. On the other hand, respiration, primarily within mitochondria, is a major source of reactive oxygen species (ROS). ROS are highly active molecules, which act as pro-oxidant.[6] By damaging DNA and proteins, they contribute to killing invading microbes and inducing inflammation, but when produced in excess and not counterbalanced, they induce cell damage and apoptosis. Therefore, pro-oxidant effects of ROS must be counterbalanced by a series of natural antioxidants, including vitamins C and E, glutathione and other such nutrients.[6] Imbalance in the equilibrium between ROS production and antioxidant systems leads to oxidative stress.[6] Oxidative stress may result either because of an overproduction of ROS or because of the insufficiency/depletion of antioxidant systems. The development of oxidative stress is clinically relevant since it is thought to contribute to organ failure.[7] Indeed, oxidative stress is associated with injury to major organs and systems, since it exerts adverse cardiac,[8] neurologic,[9] renal,[10] pulmonary[11] and haematologic[12] effects.

Lipid peroxidation is a determinant of oxidative stress.[13] Omega-6 and omega-3 fatty acids are preferential targets for free radical attack and lipid peroxidation because of their multiple double bonds,[14] and the hydroperoxide formed may oxidise proteins and DNA. On the other hand, the single double bond characterising omega-9 fatty acids makes them less prone to lipid peroxidation. In-vitro studies have shown that the production of ROS, a marker of oxidative stress, is influenced by the type of fatty acids, being higher when polyunsaturated fatty acids are used as substrate when compared with monounsaturated fatty acids.[15,16] The clinical relevance of this differential influence on oxidative stress still needs to be completely elucidated. However, Goulet et al. showed that VLDL and LDL peroxidation in paediatric patients receiving long-term PN was reduced when lipid emulsions rich in omega-9 fatty acids vs omega-6 fatty acids were used.[17]

Inflammatory and immune response

Fatty acids influence the inflammatory and immune response by their incorporation into cell membranes, and thus modulating gene expression, membrane fluidity and exposure of receptors on the cell surface.[1] Omega-3 and omega-6 fatty acids may compete for the same enzymes for metabolism in a state of enzyme saturation.[1] The products formed from omega-3 fatty acids (i.e. the odd-series eicosanoids) are typically less potent mediators of inflammation than those formed from omega-6 fatty acids (i.e. the even-series eicosanoids), whereas the metabolism of omega-9 fatty acids does not produce eicosanoids.[1] The inflammatory response is generally an adaptive, beneficial response to trauma or illness and interference with the normal host inflammatory response may prove detrimental in some patients.[18] However, it may be beneficial to modulate an exaggerated inflammatory response (i.e. as seen with sepsis). Likewise, a chronic pro-inflammatory state (i.e. in patients receiving long-term PN) may have adverse effects.

Omega-6 fatty acids have dose-dependent immunosuppressive effects. In vitro and in vivo evidence indicates that omega-6 fatty acids lead to impairment of neutrophil chemotaxis and phagocytosis[19] lymphocyte proliferation and reactivity,[20] natural killer (NK) and lymphokine-activated killer cell activities[21] as well as monocyte chemotaxis and proliferation.[22] Furthermore, administration of omega-6 polyunsaturated fatty acids has been associated with prolonged graft survival in animal transplant models[23] When given in excess, omega-3 fatty acids may have an immunosuppressive effect,[24] but perhaps the ratio of omega-6 to omega-3 may be important in determining the extent of immunosuppression.[25] Omega-3 polyunsaturated fatty acids are also generally regarded as anti-inflammatory. In addition to shifting eicosanoid production toward those that are less pro-inflammatory, omega-3 polyunsaturated fatty acids may suppress inflammation through production of resolvins and protectins (which facilitate resolution of inflammation) and through regulation of gene expression (i.e. cytokine expression).[1] Clinical studies have demonstrated favorable changes in the fatty acid and eicosanoid profiles of surgical patients receiving fish oil-containing versus soybean oil-based lipid emulsions.[26] Similar benefits have been observed in septic patients in a study which used fish oil alone at a dose that was more than 3 times greater than the recommended maximum dose.[27] In contrast, omega-9 monounsaturated fatty acids have shown limited to no impact on lymphocyte proliferation or NK cell activity in vitro or ex vivo. [28,29]

Lipid emulsions in clinical practice

For many years, PN has been considered as a life saving and effective tool to feed patients who cannot eat. In this light, lipids were regarded as a mere energy-dense source. It is now clear that many nutrients, and specifically amino acids (i.e. glutamine, leucine, arginine,) and lipids, do exert metabolic effects. It is therefore reasonable to propose that such essential nutrients as lipids should be prescribed to patients in order to nutritionally support them and influence their metabolism, in order to facilitate healing and recovery. Actually, many examples can be taken from animal biology, supporting the efficacy of changes of dietary habits in priming specific metabolic pathways to better prepare animals to significant challenges. In this respect, the dietary behaviour of the semipalmated sandpiper (*Calidris pusilla*) before autumn migration is extraordinary. In preparation for the long flight from Canada to South America, this shorebird is able to enhance the energy efficiency of its wing muscles by acutely changing its diet and thus eating almost exclusively omega-3 rich mud shrimps.[30] During the last centuries, human beings have lost their ability of selecting specific foods to better fight disease, but it is now possible to start considering the metabolic profile of the patients as a criterion according to which specific lipid emulsions should be

prescribed. Trauma is associated with an inflammatory response which is necessary to trigger the immune response. An exaggerated inflammatory response may increase the risk for complications, delayed recovery and even increased mortality. However, excessive inhibition of the inflammatory response via pharmacological or nutritional means may be equally detrimental. Indeed, Namas et al have recently demonstrated in trauma/haemorrhage patients that an adequately robust early inflammatory response is a hallmark of survival.[18]

It is therefore advisable that in clinical practice, lipid emulsions should not be considered as interchangeable and their metabolic effects should be taken into consideration. In patients in whom a robust inflammatory response is desirable, omega-6 fatty acids may be preferred. In clinical conditions where attenuation of inflammatory response is clinically meaningful, then omega-3 fatty acids should be considered. When perturbation of the physiologic inflammatory and immune response and/or exacerbation of oxidative stress could be associated with increased risk of complications, then omega-9 fatty acids may be preferred.

Based on our better knowledge on the metabolic effects of lipid emulsions, it is now tempting to speculate their use as "drugs" could provide an adequate amount of immuno-modulating fatty acids on top of the calculated energy needs. In this context, omega-9 fatty acids could be provided as the energy source because of their "immuno-neutrality", while omega-3 and omega-6 fatty acids could be provided as metabolic modulators. It is acknowledged that the available literature cannot yet support this approach, but it can also not be denied that such an approach would favourably exploit the potential clinical benefit of lipid emulsions. While waiting for clinical trials addressing the feasibility and relevance of this approach, it is important to be reminded that in matters concerning lipid emulsions "one size may not fit all (patients)".

References

1. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 2007;85:1171–84.
2. Kirchner H, Gutierrez JA, Solenberg PJ, et al. GOAT links dietary lipids with the endocrine control of energy balance. Nat Med 2009;15:741–5.
3. Bozzetti F, Forbes A. The ESPEN clinical practice guidelines on Parnetral Nutrition: present status and perspectives for future research. Clin Nutr 2009;28:359–64.
4. Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control with insulin in the ICU: facts and controversies. Chest 2007;132:268–78.
5. Lin LY, Lin HC, Lee PC, Ma WY, Lin HD. Hyperglycemia correlates with outcomes in patients receiving total parenteral nutrition. Am J Med Sci 2007;333:261–5.
6. Sies H. Oxidative stress: from basic research to clinical applications. Am J Med 1991;91:31S–38S.
7. MacDonald J, Galley HF, Webster NR. Oxidative stress and gene expression in sepsis. Br J Anaesth 2003;90:221–232.
8. Yesilbursa D, Serdar A, Senturk T, Serdar Z, Sag S, Cordan J. Effect of N-acetylcysteine on oxidative stress and ventricular function in patients with myocardial infarction. Heart Vessels 2006;21:33–37.
9. Endo H, Nito C, Kamada H, Yu F, Chan PH. Reduction in oxidative stress by superoxide dismutase overexpression attenuates acute brain injury after subarachnoid hemorrhage via activation of Akt/glycogen synthase kinase-3beta survival signaling. J Cereb Blood Flow Metab 2007;27:975–982.
10. Himmelfarb J, McMonagle E, Freedman S, et al. Oxidative stress is increased in critically ill patients with acute renal failure. J Am Soc Nephrol 2004;15:2449–56.
11. Hammerschmidt S, Wahn H. The oxidants hypochorite and hydrogen peroxide induce distinct patterns of acute lung injury. Biochim Biophys Acta 2004;1690:258–64.
12. Ambrosio G, Tritto I, Golino P. Reactive oxygen metabolites and arterial thrombosis. Cardiovasc Res 1997;34:445–52.
13. Biesalski HK. Vitamin E requirements in parenteral nutrition. Gastroenterology 2009;137:S92–S104.
14. Eritsland J. Safety considerations of polyunsaturated fatty acids. Am J Clin Nutr 2000;71:197S–201S.
15. Watkins SM, Carter LC, German JB. Docosahexaenoic acid accumulates in cardiolipin and enhances HT-29 cell oxidant production. J Lipid Res 1998;39:1583–8.
16. Tirosh O, Ilan E, Anavi S, Ramadori G, Madar Z. Nutritional lipid-induced oxidative stress leads to mitochondrial dysfunction followed by necrotic death in FaO hepatocytes. Nutrition 2009;25:200–8.
17. Goulet O, de Potter S, Antebi H, et al. Long-term efficacy and safety of a new olive oil-based fat emulsion in pediatric patients: a double-blind randomized study. Am J Clin Nutr 1999;70:338–45.
18. Namas R, Ghuma A, Torres A, et al. An adequately robust early TNF-a response is a hallmark of survival following trauma/hemorrhage. PLoS ONE 2009;4:e8406.
19. Wiernik A, Jarstrand C, Julander I. The effect of intralipid on mononuclear and polymorphonuclear phagocytes. Am J Clin Nutr 1983;37:256–61.
20. Sedman PC, Ramsden CW, Brennan TG, Guilou PJ. Pharmacological concentrations of lipid emulsions inhibit interleukin-2 dependent lymphocyte responses in vitro. JPEN 1990;14:12–7.
21. Sedman PC, Somers SS, Ramsden CW, Brennan TG, Guilou PJ. Effects of different lipid emulsions on lymphocyte function during total parenteral nutrition. Br J Surg. 1991;78:1396–9.
22. Fraser I, Neoptolemos J, Woods P, Bowry V, Bell PR. The effect of intralipid on human lymphocyte and monocyte function. Clin Nutr 1983;2:37–40.
23. Grimm H, Tibell A, Norrlind B, Schott J, Bohle RM. Nutrition and allorejection impact of lipids. Transpl Immunol 1995;3:62–7.
24. Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. JPEN 2006;30:351–67.
25. Grimm H, Tibell A, Norrlind B, Blecher C, Wilker S, Schwemmie K. Immunoregulation by parenteral lipids: impact of the n-3 to n-6 fatty acid ratio. JPEN 1994;18:417–21.
26. Morlion BJ, Torwesten E, Lessire H, Sturm G, Peskar BM, Furst P, Puchstein C. The effect of parenteral fish oil on leukocyte membrane fatty acid composition and leukotriene-synthesizing capacity in patients with postoperative trauma. Metabolism 1996;45:1208–13.
27. Mayer K, Fegbeutel C, Hattar K, et al. Omega-3 vs omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. Intensive Care Med 2003;29:1472–81.
28. Granato D, Blum S, Rossle C, Le Boucher J, Malnoe A, Dutot G. Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro. JPEN 2000;24:113–8.
29. Yaqoob P, Knapper JA, Webb DH, Williams CM, Newsholme EA, Calder PC. Effect of olive oil on immune function in middle-aged men. Am J Clin Nutr 1998;67:129–35.
30. Maillet D, Weber J-M. Relationship between n-3 PUFA content and energy metabolism in the flight muscles of a migrating shorebird: evidence for natural doping. J Exp Biol 2007;210:413–20.

Optimal composition of intravenous lipids

Kreymann G
Baxter Healthcare, Deerfield, IL, USA
Correspondence to: Dr Georg Kreymann, e-mail: georg_kreymann@baxter.com

Abstract

The provision of energy from a lipid source is an essential component of any parenteral nutrition (PN) therapeutic regimen in the appropriate clinical setting. All available sources of intravenous lipid emulsions have a low osmolarity but they strongly differ in their immunologic effects and their effects on oxidative stress, liver injury and mitochondrial function. The ω–9/ω–6 lipid emulsion with its relative immune-neutrality and also the newer fish oil admixtures are lipid emulsions that can be used in most critically ill and non-critically ill patients. Despite extensive research and encouraging progress in the availability of such lipid emulsions, there is still need for a lipid emulsions that could be advantageous in patients with real hyperinflammation.

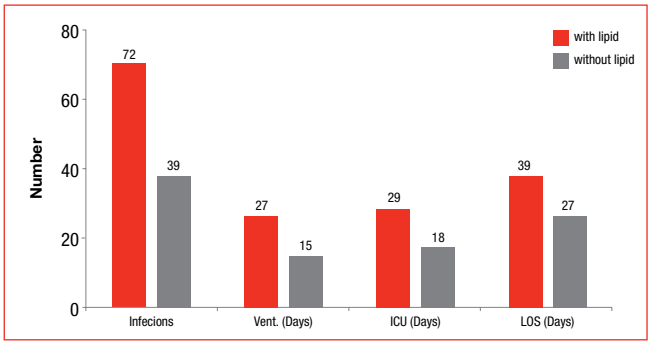
S Afr J Clin Nutr 2010;23(1) Supplement:S11-S14

The composition of an intravenous (IV) lipid emulsion is of great importance in parenteral nutrition (PN) therapy, as most of its effects depend on the kind of fatty acids included and their respective ratio to each other. Today´s lipid emulsions may include four classes of different fatty acids (FA), namely ω–6 long chain polyunsaturated fatty acids, ω–3 long chain polyunsaturated fatty acids, ω–9 long chain monounsaturated fatty acids and medium chain saturated fatty acids. All these fatty acids present a source of energy with a low osmolarity but they strongly differ in their immunologic effects and their effects on oxidative stress, liver injury and mitochondrial function. For this review the effects of the different admixtures will be discussed following the time line of their landmark introduction into clinical practice.

The first lipid emulsion for parenteral application was a 100% soy bean oil-based emulsion introduced in 1961. There were two reasons for the development of this type of lipid emulsion. Firstly, soy bean oil contains the two essential ω–6 fatty acids, linoleic acid and linolenic acids, and secondly, soy bean oil was readily available. Very soon after its introduction into clinical practice its immunologic properties came into discussion[1] and with its widespread use concerns were raised regarding its immune-compromising effects and the increased risk of infections.[2,3] Today, there is consistent evidence from human and animal *in vitro* and *ex vivo* studies showing that ω–6 fatty acids or a soy bean oil-based emulsion inhibit lymphocyte proliferation,[4,5] decrease natural and lymphokine activated killer cell acitivity,[6,7] decrease chemotaxis and random migration of granulocytes[8–10] and negatively affect the reticuloendothelial system.[11,12]

Despite these impressive experimental results, some smaller trials in malnourished or paediatric patients[13–15] and one large clinical trial in bone marrow transplanted patients[16] found no significant difference between patients who received a parenteral ω–6 emulsion and those who did not. One smaller crossover study even reported an immunorestorative effect of the lipid emulsion.[17] In contrast, the study reported by Battistella[18] randomised 60 trauma patients with a severity score of 27 and an APACHE II score of 23 to 10 days of postoperative PN with our without an ω–6 emulsion. Patients who received the lipid emulsion had a longer length of hospitalisation (39 vs 27 days), a longer length of stay in the intensive care unit (29 vs 18 days) and more days of mechanical ventilation (27 vs 15) (Figure 1) The group which received the lipid emulsion also had a significantly reduced natural and lymphokine activated killer cell activity and a higher number of infections (72 vs 39). Although this trial is somewhat biased by the fact that the group which did not receive the lipid emulsion also received 25% less energy, these negative results made the Canadian, the European and also the American guideline committee recommend that – at least – intensive care patients should not receive pure ω–6 lipid emulsions as part of their PN regimens.

Figure 1: Battistella FD et al. Lipid emulsion in trauma victims (Figure was created using data from this publication)[18]



In order to reduce the amount of ω–6 fatty acids in a lipid emulsion, medium chain triglycerides were introduced into clinical practice in 1984. These fatty acids with a chain length of 8 resp. 10 carbon atoms are derived from coconut oil. *In vitro* and *ex vivo* studies could show that a 50/50 admixture of ω–6 FA and MCT (ω–6/MCT) could prevent the inhibition of lymphocyte proliferation,[19] that natural killer cell activity was less reduced,[20] and that the expression of adhesion molecules [21,22] as well as the phagocytic capacity of the RES were increased.[23,24] On the other hand it was also shown that the phagocytic capacity for *C. albicans* was significantly reduced.[25,26]

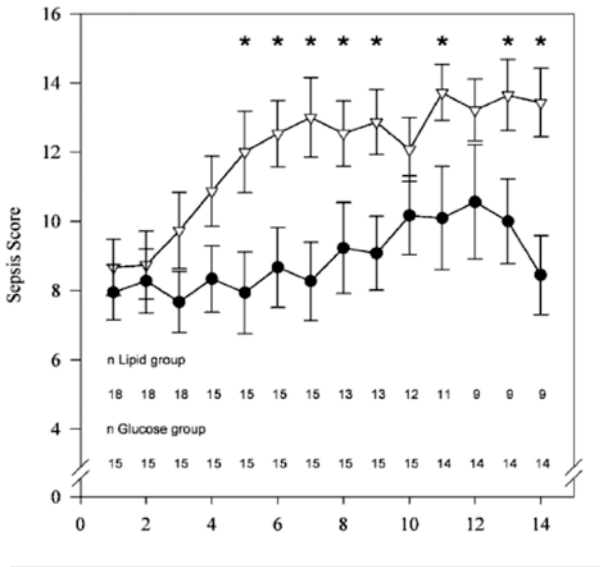
Seven smaller trials[19,27–32] in patients with ARDS, acquired immune deficiency syndrome, sepsis or undefined critically ill patients showed no significant difference in any important outcome parameter. One of two medium size trials (n = 72) showed less intra-abdominal infections and a trend towards reduced mortality in malnourished surgical patients[33] and the other one a significantly greater rise in retinol binding protein and nitrogen balance in septic patients.[34] However, as there are no harmful results, ω–6/MCT lipid emulsions are still in use and may still be used in critically ill patients.

The next step in the development of intravenous lipid emulsions was a further reduction in the ω–6 FA content to 20% and the completion with ω–9 oleic acid from olive oil (OO) – which was introduced in 1996. The concern with this new emulsion was that the low content of ω–6 FA might lead to a deficiency in essential FAs. This concern was partly addressed by a study in children reported by Munck[35] which documented that such a lipid emulsion could reduce the C20:3 content – a sign of essential acid deficiency – over 15 days as well as ω–6 FA. There are also experimental studies that showed that ω–9 FA or a lipid emulsion based on ω–9 FA (ω–9/ω–6) did not inhibit lymphocyte proliferation,[35,36] did not reduce the expression of activation markers on granulocytes[21,35,37] and that it had almost no effect on the release of proinflammatory cytokines.[38–41] Thus, its effect on most immunologic parameters was almost neutral.

This ω–9/ω–6 emulsion was evaluated in six trials in preterm infants[42–48] and in three trials in paediatric patients.[35,49–51] All trials showed a good short and (some studies) long term tolerability and no signs of essential fatty acid deficiency. In adults, this ω–9/ω–6 emulsion was administered over three to six months in home parenteral nutrition.[52–54] Besides seven mostly smaller trials in various patients, this emulsion was also studied in one observational[55] and two controlled trials[56,57] in critically ill patients. The trial reported by Huschak[57] randomised 33 severe multiple trauma patients to either high dose ω–9/ω–6 (75% of non-protein energy) or normal dose ω–6 FA (37% of non-protein energy). They found a significant shorter length of ventilation and a significantly shorter length of stay in the ICU in the high dose ω–9/ω–6 group (Figure 2). The trial reported by Garcia-de-Lorenzo[56] also found significantly less abnormalities in liver function in the ω–9/ω–6 group.

The next lipid emulsion – introduced in 1991 – was based on ω–3 fatty acids derived from fish oil (FO). In many *in vitro* and *ex vivo* studies it could be shown that ω–3 fatty acids had strong anti-inflammatory and immunosuppressive effects, already documented in various diseases such as rheumatoid arthritis, inflammatory bowel disease and asthma. Thus lipid emulsion inhibited lymphocyte proliferation,[58–61] decreased natural killer cell activity[6,62] as well as monocyte chemiluminescence, chemotaxis and adhesion to

Figure 2 : Huschak G et al.[57] Olive oil based nutrition in multiple trauma patients



	Lipid group (*n*=18)	Glucose group (*n*=15)	*p*[a]
Length of mechanical ventilation (days)	13.0±8.9 (3–35)	20.4±7.0 (9–29)	0.01
Length of stay in the ICU (days)	17.9±11.2 (3–42)	25.1±7.0 (12–37)	0.04
Length of stay in the acute care hospital (days)	80.4±84.4 (3–274)	84.5±71.7 (26–297)	0.88

[a] Student's *t* test

endothelial cells[63–65] and it reduced the release of proinflammatory cytokines.[66–68]

As the ω–3 fatty acids emulsion (ω–3) was never licensed for a standalone use but had to be administered in addition to another lipid emulsion, there are only few experimental clinical studies on the use of pure ω–3.[69–71] In these, its main effect was to modulate cytokine and leukotriene release (Figure 3).

As far as the admixture of ω–3 to other lipids is concerned, an important experiment was performed by Grimm et al[72] in 1994. They performed allogenic heart transplantations in inbred rats and fed them postoperatively with different lipid emulsions: fish oil, soybean oil, safflower oil or a mixture of safflower with fish oil with a ratio of 2.1:1. The rejection time of the allograft was significantly prolonged with fish oil but also with safflower or soybean oil. However, the mixture of safflower with fish oil induced a rejection time which was comparable to control animals (Figure 4). This experiment was the base for the ω–6:ω–3 ratio in the supplemental use of ω–3 with ω–6 and also for all lipid emulsions containing fish oil which were introduced after 2005.

It might be concluded from these data that an admixture with the described ω–6:ω–3 ratio is mostly immune-neutral. However, experimental data on the immunologic effect of these latest lipid emulsions are very rare. De Nardi et al[73] found yet a significant increase in macrophages that had engaged in phagocytosis with ω–6/MCT and ω–6/MCT/FO. However, there was no increase with ω–6/MCT/FO/OO.

There are many clinical studies concerning the addition of fish oil to lipid emulsions. They can be divided into studies using the admixture of pure ω–3 to other lipids, studies using ω–6/MCT/FO, or studies using ω–6/MCT/FO/OO.

Figure 3 : Meyer K et al.[67] Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis

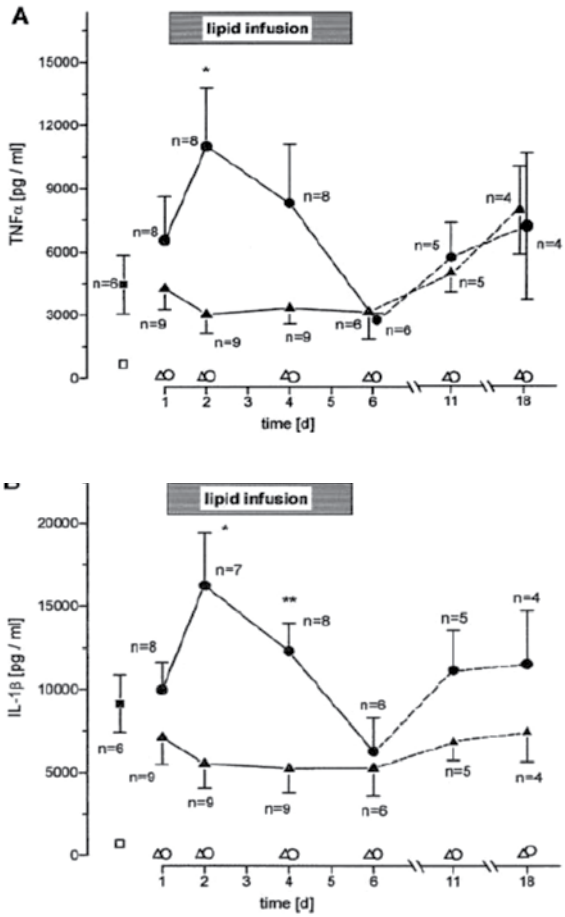
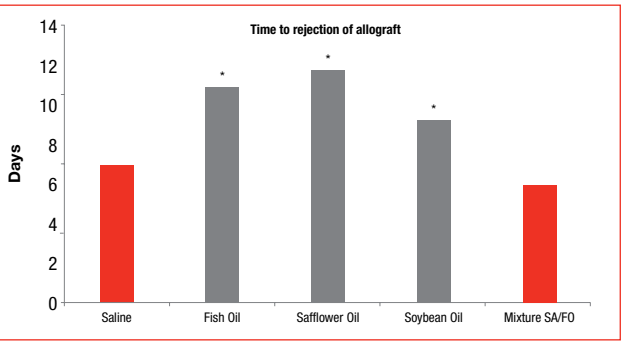


Figure 4: Grimm H et al.[72] Immunoregulation by parenteral lipids (Figure was created using data from this publication)



There are two observational[74,75] and nine randomised controlled[76–83] trials on the admixture of pure ω–3 FA to other lipids. While none of the randomised trials showed a significant improvement in survival or length of stay, the observational trial reported by Heller et al[74] showed that FO had the most favorable effects on survival, infection rates and length of stay when administered in doses between 0.1 and 0.2 g/kg/day.

The eight studies which evaluated ω–6/MCT/FO[84–91] also didn't show any significant effect on outcome except the trial reported by Wichmann et al[87] which showed a significant decrease in the length of stay (17.2 vs 21.9 days).

Of the three studies evaluating ω–6/MCT/FO/OO,[92–94] the study reported by Mertes et al[93] showed a trend towards a reduced length of hospital stay (15.7 +/- 6.3 vs 17.8 +/- 13.2 days). Piper et al[92] compared ω–6/MCT/FO/OO to ω–9/ω–6 and found at day two and five significantly lower levels of liver enzymes in the ω–6/MCT/FO/OO group. However, the importance of this result is limited by the fact that the higher levels found with ω–9/ω–6 also were only slightly above normal range.

In conclusion, ω–9/ω–6 with its relative immune-neutrality is a lipid emulsion that can be used in most critically ill and non-critically ill patients. The addition of fish oil in the newer ω–6/MCT/FO or ω–6/MCT/FO/OO emulsions certainly has advantages compared to pure ω–6 or ω–6/MCT and these emulsions can also be used in most patients. However, the drawback is that the immune-modulatory potential of these emulsions is rather low as the fish oil content is too low to exert a greater effect. So there is still need for a lipid emulsion that could be advantageous in patients with real hyperinflammation.

References

1. Mertin J, Hunt R. Influence of polyunsaturated fatty acids on survival of skin allografts and tumor incidence in mice. Proc Natl Acad Sci U S A 1976;73(3):928–931.
2. Wan JM, Teo TC, Babayan VK, Blackburn GL. Invited comment: lipids and the development of immune dysfunction and infection. JPEN J Parent Ent Nutrition 1988;12(6 Suppl):43S–52S.
3. Utermohlen V, Tucker MA. Possible effects of dietary n-6 series polyunsaturated fatty acids on the development of immune dysfunction and infection. Proc Nutr Soc 1986;45(3):327–331.
4. Calder PC, Sherrington EJ, Askanazi J, Newsholme EA. Inhibition of lymphocyte proliferation in vitro by two lipid emulsions with different fatty acid compositions. Clin Nutr 1994;13(2):69–74.
5. Soyland E, Nenseter MS, Braathen L, Drevon CA. Very long chain n-3 and n-6 polyunsaturated fatty acids inhibit proliferation of human T-lymphocytes in vitro. Eur J Clin Invest 1993;23(2):112–121.
6. Yaqoob P, Newsholme EA, Calder PC. Inhibition of natural killer cell activity by dietary lipids. Immunol Lett 1994;41(2–3):241–247.
7. Monson JR, Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Total parenteral nutrition adversely influences tumour-directed cellular cytotoxic responses in patients with gastrointestinal cancer. Eur J Surg Oncol 1988;14(5):935–943.
8. Cury-Boaventura MF, Gorjao R, de Lima TM et al. Toxicity of a soybean oil emulsion on human lymphocytes and neutrophils. JPEN J Parenter Enteral Nutr 2006;30:115–123.
9. Fischer GW, Hunter KW, Wilson SR, Mease AD. Diminished bacterial defences with intralipid. Lancet 1980;2:819–820.
10. Nordenstrom J, Jarstrand C, Wiernik A. Decreased chemotactic and random migration of leukocytes during Intralipid infusion. Am J Clin Nutr 1979;32:2416–2422.
11. Katz S, Plaisier BR, Folkening WJ, Grosfeld JL. Intralipid adversely affects reticuloendothelial bacterial clearance. J Pediatr Surg 1991;26(8):921–924.
12. Seidner DL, Mascioli EA, Istfan NW et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. JPEN J Parenter Enteral Nutr 1989;13:614–619.
13. Li X, Ying J, Zeng S et al. The effects of a short-term long-chain-triglyceride infusion on the postoperative immune function of pediatric patients receiving a gastrointestinal surgical procedure. JPEN J Parenter Enteral Nutr 2008;32(1):72–77.
14. Dionigi P, Dionigi R, Prati U, et al. Effect of Intralipid(Reg.trademark) on some immunological parameters and leukocyte functions in patients with esophageal and gastric cancer. Clin Nutrition 1985;4(4):229–234.
15. Ota DM, Jessup JM, Babcock GF et al. Immune function during intravenous administration of a soybean oil emulsion. JPEN J Parenter Enteral Nutr 1985;9(1):23–27.
16. Lenssen P, Bruemmer BA, Bowden RA, Gooley T, Aker SN, Mattson D. Intravenous lipid dose and incidence of bacteremia and fungemia in patients undergoing bone marrow transplantation. Am J Clin Nutr 1998;67(5):927–933.
17. Monson JR, Ramsden CW, MacFie J, Brennan TG, Guillou PJ. Immunorestorative effect of lipid emulsions during total parenteral nutrition. Br J Surg 1986;73:843–846.
18. Battistella FD, Widergren JT, Anderson JT, Siepler JK, Weber JC, MacColl K. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. J Trauma 1997;43(1):52–58.
19. Gelas P, Cotte L, Poitevin-Later F et al. Effect of parenteral medium- and long-chain triglycerides on lymphocytes subpopulations and functions in patients with acquired immunodeficiency syndrome: a prospective study. JPEN J Parent Ent Nutrition 1998;22(2):67–71.
20. Sedman PC, Ramsden CW, Brennan TG, Guillou PJ. Pharmacological concentrations of lipid emulsions inhibit interleukin-2-dependent lymphocyte responses in vitro. JPEN J Parenter Enteral Nutr 1990;14(1):12–17.
21. Versleijen M, Roelofs H, Preijers F, Roos D, Wanten G. Parenteral lipids modulate leukocyte phenotypes in whole blood, depending on their fatty acid composition. Clin Nutr 2005;24(5):822–829.
22. Wanten GJ, Roos D, Naber AH. Effects of structurally different lipid emulsions on human neutrophil migration. Clin Nutr 2000;19:327–331.
23. Hamawy KJ, Moldawer LL, Georgieff M et al. The Henry M. Vars Award. The effect of lipid emulsions on reticuloendothelial system function in the injured animal. JPEN J Parent Ent Nutrition 1985;9(5):559–565.
24. Sobrado J, Moldawer LL, Pomposelli JJ et al. Lipid emulsions and reticuloendothelial system function in healthy and burned guinea pigs. Am J Clin Nutr 1985;42:855–863.
25. Wanten GJ, Netea MG, Naber TH et al. Parenteral administration of medium- but not long-chain lipid emulsions may increase the risk for infections by Candida albicans. Infect Immun 2002;70(11):6471–6474.
26. Wanten GJ, Curfs JH, Meis JF, Naber AH. Phagocytosis and killing of Candida albicans by human

neutrophils after exposure to structurally different lipid emulsions. JPEN J Parenter Enteral Nutr 2001;25(1):9–13.
27. Iovinelli G, Marinangeli F, Ciccone A et al. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. Minerva Anestesiol 2007;73(1–2):65–76.
28. Lekka ME, Liokatis S, Nathanail C, Galani V, Nakos G. The impact of intravenous fat emulsion administration in acute lung injury. Am J Respir Crit Care Med 2004;169(5):638–644.
29. Masclans JR, Iglesia R, Bermejo B, Pico M, Rodriguez-Roisin R, Planas M. Gas exchange and pulmonary haemodynamic responses to fat emulsions in acute respiratory distress syndrome. Int Care Med 1998;24(9):918–923.
30. Ball MJ. Parenteral nutrition in the critically ill: use of a medium chain triglyceride emulsion. Intensive Care Med 1993;19(2):89–95.
31. Radermacher P, Santak B, Strobach H, Schror K, Tarnow J. Fat emulsions containing medium chain triglycerides in patients with sepsis syndrome: effects on pulmonary hemodynamics and gas exchange. Int Care Med 1992;18(4):231–234.
32. Ball MJ, White K. Comparison of medium and long chain triglyceride metabolism in intensive care patients on parenteral nutrition. Intensive Care Med 1989;15(4):250–254.
33. Grau T, Ruiz de Adana JC, Zubillaga S, Fuerte S, Giron C. [Randomized study of two different fat emulsions in total parenteral nutrition of malnourished surgical patients;effect of infectious morbidity and mortality]. Nutr Hosp 2003;18(3):159–166.
34. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ et al. Clinical and metabolic effects of two lipid emulsions on the parenteral nutrition of septic patients. Nutrition 2002;18(2):134–138.
35. Munck A, Navarro J. Tolerability and efficacy of ClinOleic® lipid emulsion in children reliant exclusively on parenteral nutrition. Nutr Clin Métabol 1996;10:45S–47S.
36. Granato D, Blum S, Rossle C, Le Boucher J, Malnoe A, Dutot G. Effects of parenteral lipid emulsions with different fatty acid composition on immune cell functions in vitro. JPEN J Parent Ent Nutrition 2000;24(2):113–118.
37. Buenestado A, Cortijo J, Sanz MJ et al. Olive oil-based lipid emulsion's neutral effects on neutrophil functions and leukocyte-endothelial cell interactions. JPEN J Parenter Enteral Nutr 2006;30(4):286–296.
38. Leite MS, Pacheco P, Gomes RN et al. Mechanisms of increased survival after lipopolysaccharide-induced endotoxic shock in mice consuming olive oil-enriched diet. Shock 2005;23(2):173–178.
39. Reimund JM, Scheer O, Muller CD, Pinna G, Duclos B, Baumann R. In vitro modulation of inflammatory cytokine production by three lipid emulsions with different fatty acid compositions. Clin Nutr 2004;23(6):1324–1332.
40. Sadeghi S, Wallace FA, Calder PC. Dietary lipids modify the cytokine response to bacterial lipopolysaccharide in mice. Immunology 1999;96(3):404–410.
41. Yaqoob P, Calder P. Effects of dietary lipid manipulation upon inflammatory mediator production by murine macrophages. Cell Immunol 1995;163(1):120–128.
42. Deshpande GC, Simmer K, Mori T, Croft K. Parenteral lipid emulsions based on olive oil compared with soybean oil in preterm (<28 weeks' gestation) neonates: a randomised controlled trial. J Pediatr Gastroenterol Nutr 2009;49:619–625.
43. Roggero P, Mosca F, Gianni ML et al. F2-isoprostanes and total radical-trapping antioxidant potential in preterm infants receiving parenteral lipid emulsions. Nutrition 2009.
44. Gawecka A, Michalkiewicz J, Kornacka MK, Luckiewicz B, Kubiszewska I. Immunologic properties differ in preterm infants fed olive oil vs soy-based lipid emulsions during parenteral nutrition. JPEN J Parenter Enteral Nutr 2008;32(4):448–453.
45. Webb AN, Hardy P, Peterkin M et al. Tolerability and safety of olive oil-based lipid emulsion in critically ill neonates: a blinded randomized trial. Nutrition 2008;24(11–12):1057–1064.
46. van Kempen AA, van der Crabben SN, Ackermans MT, Endert E, Kok JH, Sauerwein HP. Stimulation of gluconeogenesis by intravenous lipids in preterm infants: response depends on fatty acid profile. Am J Physiol Endocrinol Metab 2006;290(4):E723–E730.
47. Pitkänen OM, Luukkainen P, Andersson S. Attenuated lipid peroxidation in preterm infants during subsequent doses of intravenous lipids. Biol Neonate 2004;85(3):184–187.
48. Göbel Y, Koletzko B, Bohles HJ et al. Parenteral fat emulsions based on olive and soybean oils: a randomized clinical trial in preterm infants. J Pediatr Gastroenterol Nutr 2003;37(2):161–167.
49. Hartman C, Ben-Artzi E, Berkowitz D et al. Olive oil-based intravenous lipid emulsion in pediatric patients undergoing bone marrow transplantation: A short-term prospective controlled trial. Clin Nutr 2009.
50. Goulet O, de Potter S, Antebi H et al. Long-term efficacy and safety of a new olive oil-based intravenous fat emulsion in pediatric patients: a double-blind randomized study. Am J Clin Nutr 1999;70(3):338–345.
51. Antébi H, Zimmerman L, Bourcier C et al. Peroxydation *in vitro* et effet de l´administration en nutrition parentérale totale d´une émulsion lipidique à base d'huile d´olive sur la peroxydabilité des lipoprotéines de basse densité chez l´enfant. Nutr Clin Métabol 1996;10:41S–43S.
52. Reimund JM, Rahmi G, Escalin G et al. Efficacy and safety of an olive oil-based intravenous fat emulsion in adult patients on home parenteral nutrition. Aliment Pharmacol Ther 2005;21(4):445–454.
53. Vahedi K, Atlan P, Joly F et al. A 3-month double-blind randomised study comparing an olive oil- with a soyabean oil-based intravenous lipid emulsion in home parenteral nutrition patients. Br J Nutr 2005;94(6):909–916.
54. Thomas-Gibson S, Jawhari A, Atlan P, Brun AL, Farthing M, Forbes A. Safe and efficacious prolonged use of an olive oil-based lipid emulsion (ClinOleic) in chronic intestinal failure. Clin Nutr 2004;23(4):697–703.
55. Mateu-de Antonio J, Grau S, Luque S, Marin-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. Br J Nutr 2008;99(4):846–854.
56. Garcia-de-Lorenzo A, Denia R, Atlan P et al. Parenteral nutrition providing a restricted amount of linoleic acid in severely burned patients: a randomised double-blind study of an olive oil-based lipid emulsion v. medium/long-chain triacylglycerols. Br J Nutr 2005;94(2):221–230.
57. Huschak G, Zur NK, Hoell T, Riemann D, Mast H, Stuttmann R. Olive oil based nutrition in multiple trauma patients: a pilot study. Intensive Care Med 2005;31(9):1202–1208.
58. Endres S, Meydani SN, Ghorbani R, Schindler R, Dinarello CA. Dietary supplementation with n-3 fatty acids suppresses interleukin-2 production and mononuclear cell proliferation. J Leukoc Biol 1993;54:599–603.
59. Kelley DS, Branch LB, Love JE, Taylor PC, Rivera YM, Iacono JM. Dietary alpha-linolenic acid and immunocompetence in humans. Am J Clin Nutr 1991;53:40–46.
60. Meydani SN, Endres S, Woods MM et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. J Nutr 1991;121:547–555.
61. Molvig J, Pociot F, Worsaae H et al. Dietary supplementation with omega-3-polyunsaturated fatty acids decreases mononuclear cell proliferation and interleukin-1 beta content but not monokine secretion in healthy and insulin-dependent diabetic individuals. Scand J Immunol 1991;34:399–410.
62. Kelley DS, Taylor PC, Nelson GJ et al. Docosahexaenoic acid ingestion inhibits natural killer cell activity and production of inflammatory mediators in young healthy men. Lipids 1999;34:317–324.
63. Mayer K, Merfels M, Muhly-Reinholz M et al. Omega-3 fatty acids suppress monocyte adhesion to human endothelial cells: role of endothelial PAF generation. Am J Physiol Heart Circ Physiol 2002;283(2):H811–H818.
64. Fisher M, Levine PH, Weiner BH et al. Dietary n-3 fatty acid supplementation reduces superoxide production and chemiluminescence in a monocyte-enriched preparation of leukocytes. Am J Clin Nutr 1990;51:804–808.
65. Schmidt EB, Pedersen JO, Ekelund S, Grunnet N, Jersild C, Dyerberg J. Cod liver oil inhibits neutrophil and monocyte chemotaxis in healthy males. Atherosclerosis 1989;77:53–57.
66. Pluess TT, Hayoz D, Berger MM et al. Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. Intensive Care Med 2007;33(5):789–797.
67. Mayer K, Meyer S, Reinholz-Muhly M et al. Short-time infusion of fish oil-based lipid emulsions, approved for parenteral nutrition, reduces monocyte proinflammatory cytokine generation and adhesive interaction with endothelium in humans. J Immunol 2003;171(9):4837–4843.
68. Endres S, Ghorbani R, Kelley VE et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265–271.
69. Mayer K, Fegbeutel C, Hattar K et al. Omega-3 vs. omega-6 lipid emulsions exert differential influence on neutrophils in septic shock patients: impact on plasma fatty acids and lipid mediator generation. Intensive Care Med 2003;29(9):1472–1481.
70. Mayer K, Gokorsch S, Fegbeutel C et al. Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med 2003;167(10):1321–1328.
71. Weiss G, Meyer F, Matthies B, Pross M, Koenig W, Lippert H. Immunomodulation by perioperative administration of n-3 fatty acids. Br J Nutr 2002;87 Suppl 1:S89–S94.
72. Grimm H, Tibell A, Norrlind B, Blecher C, Wilker S, Schwemmle K. Immunoregulation by parenteral lipids: impact of the n-3 to n-6 fatty acid ratio. JPEN J Parent Ent Nutrition 1994;18(5):417–421.
73. De Nardi L, Bellinati-Pires R, Torrinhas RS, Bacchi CE, Arias V, Waitzberg DL. Effect of fish oil containing parenteral lipid emulsions on neutrophil chemotaxis and resident-macrophages' phagocytosis in rats. Clin Nutr 2008;27(2):283–288.
74. Heller AR, Rossler S, Litz RJ et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med 2006;34(4):972–979.
75. Tsekos E, Reuter C, Stehle P, Boeden G. Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. Clin Nutr 2004;23(3):325–330.
76. Liang B, Wang S, Ye YJ et al. Impact of postoperative omega-3 fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancer patients. World J Gastroenterol 2008;14(15):2434–2439.
77. Wang X, Li W, Li N, Li J. {omega}-3 Fatty Acids-Supplemented Parenteral Nutrition Decreases Hyperinflammatory Response and Attenuates Systemic Disease Sequelae in Severe Acute Pancreatitis: A Randomized and Controlled Study. JPEN J Parenter Enteral Nutr 2008;32(3):236–241.
78. Tappy L, Berger MM, Schwarz JM et al. Metabolic effects of parenteral nutrition enriched with n-3 polyunsaturated fatty acids in critically ill patients. Clin Nutr 2006;25(4):588–595.
79. Heller AR, Rossel T, Gottschlich B et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. Int J Cancer 2004;111(4):611–616.
80. Heller AR, Fischer S, Rossel T et al. Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. Br J Nutr 2002;87 Suppl 1:S95–101.
81. Schauder P, Rohn U, Schafer G, Korff G, Schenk HD. Impact of fish oil enriched total parenteral nutrition on DNA synthesis, cytokine release and receptor expression by lymphocytes in the postoperative period. Br J Nutr 2002;87 Suppl 1:S103–S110.
82. Abribat T, Nedelec B, Jobin N, Garrel DR. Decreased serum insulin-like growth factor-I in burn patients: relationship with serum insulin-like growth factor binding protein-3 proteolysis and the influence of lipid composition in nutritional support. Crit Care Med 2000;28(7):2366–2372.
83. Morlion BJ, Torwesten E, Lessire H et al. The effect of parenteral fish oil on leukocyte membrane fatty acid composition and leukotriene-synthesizing capacity in patients with postoperative trauma. Metabolism 1996;45(10):1208–1213.
84. Berger MM, Tappy L, Revelly JP et al. Fish oil after abdominal aorta aneurysm surgery. Eur J Clin Nutr 2008;62(9):1116–1122.
85. Friesecke S, Lotze C, Kohler J, Heinrich A, Felix SB, Abel P. Fish oil supplementation in the parenteral nutrition of critically ill medical patients: a randomised controlled trial. Intensive Care Med 2008;34(8):1411–1420.
86. Senkal M, Geier B, Hannemann M et al. Supplementation of omega-3 fatty acids in parenteral nutrition beneficially alters phospholipid fatty acid pattern. JPEN J Parenter Enteral Nutr 2007;31(1):12–17.
87. Wichmann MW, Thul P, Czarnetzki HD, Morlion BJ, Kemen M, Jauch KW. Evaluation of clinical safety and beneficial effects of a fish oil containing lipid emulsion (Lipoplus, MLF541): Data from a prospective, randomized, multicenter trial. Crit Care Med 2007;35:700–706.
88. Koller M, Senkal M, Kemen M, Konig W, Zumtobel V, Muhr G. Impact of omega-3 fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. Clin Nutr 2003;22(1):59–64.
89. Linseisen J, Hoffmann J, Lienhard S, Jauch KW, Wolfram G. Antioxidant status of surgical patients receiving TPN with an omega-3- fatty acid-containing lipid emulsion supplemented with alpha-tocopherol. Clin Nutr 2000;19(3):177–184.
90. Wachtler P, Konig W, Senkal M, Kemen M, Koller M. Influence of a total parenteral nutrition enriched with omega-3 fatty acids on leukotriene synthesis of peripheral leukocytes and systemic cytokine levels in patients with major surgery. J Trauma 1997;42(2):191–198.
91. Barbosa VM, Miles EA, Calhau C, Lafuente E, Calder PC. Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. Crit Care 2010;14:R5.
92. Piper SN, Schade I, Beschmann RB, Maleck WH, Boldt J, Rohm KD. Hepatocellular integrity after parenteral nutrition: comparison of a fish-oil-containing lipid emulsion with an olive-soybean oil-based lipid emulsion. Eur J Anaesthesiol 2009;26:1076–1082.
93. Mertes N, Grimm H, Furst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Ann Nutr Metab 2006;50(3):253–259.
94. Antebi H, Mansoor O, Ferrier C et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. JPEN J Parenter Enteral Nutr 2004;28(3):142–148.

Diarrhoea and malnutrition

Nel ED
Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Hospital, Cape Town, South Africa.
Correspondence to: Dr E Nel, e-mail: edn@sun.ac.za

Abstract

The relationship between diarrhoea and malnutrition is bidirectional: diarrhoea leads to malnutrition while malnutrition aggravates the course of diarrhoea. Many factors contribute to the detrimental effect of diarrhoea on nutrition. Reduced intake (due to anorexia, vomiting, and withholding of feeds), maldigestion, malabsorption, increased nutrient losses, and the effects of the inflammatory response are some of the factors involved. High volume stool losses (greater than 30 ml/kg/day) are associated with a negative balance for protein, fat, and sugar absorption. Enteric infections often cause increased loss of endogenous proteins, particularly after invasive bacterial infections. Initially, the major emphasis of treatment of acute diarrhoea in children is the prevention and treatment of dehydration, electrolyte abnormalities and comorbid conditions. The objectives of diarrhoeal disease management are to prevent weight loss, to encourage catch-up growth during recovery, to shorten the duration and to decrease the impact of the diarrhoea on the child's health. Addressing only diarrhoea or only food security is unlikely to be successful in decreasing the prevalence of malnutrition. Existing evidence provides some guidelines as to the optimal nutritional management of children with diarrhoea and novel treatments may prove to be valuable in future.

S Afr J Clin Nutr 2010;23(1) Supplement:S15-S18

Introduction

The burden of diarrhoea and malnutrition in developing countries are both high, and, as these conditions frequently coexist, it is attractive to hypothesise a causal association between them. The review, "Interactions of Nutrition and Infection" by Scrimshaw, Taylor and Gordon in 1968,[1] first drew attention to the relationship between infection and nutrition. Following this publication, studies attempted to quantify the contribution of diarrhoea to childhood malnutrition, to define the pathophysiology, to determine the appropriate nutritional therapy, and, more recently, to investigate the role of intestinal disease in HIV infected children. In this paper the interaction between diarrhoea and malnutrition in children will be reviewed briefly.

Epidemiology

The relationship between diarrhoea and malnutrition is bidirectional: diarrhoea leads to malnutrition while malnutrition aggravates the course of diarrhoea. On the one hand, severe and prolonged episodes of diarrhoea cause malnutrition in individual patients; on the other hand, malnourished children are more likely to develop complications with diarrhoea. Many studies, addressing the relationship between diarrhoea and malnutrition, have demonstrated a detrimental effect of diarrhoea on nutritional status.

Some of the first evidence of the association between diarrhoea and malnutrition was the graphical representation of the interaction between growth and infection in children in South America. Mata and co-workers[2] observed cohorts of infants born in Santa Maria Cauquè in Gautemala. Intestinal as well as other infections and growth parameters were recorded from birth to three years. Episodes of diarrhoea, upper and lower respiratory tract infection, measles and other infections were associated with progressive growth faltering: children with poor growth (growth in the lower quartile of the study) had more infections than those who grew the best (growth in the upper quartile). Especially dysentery and bronchopneumonia occurred more frequently in the lower growth quartile.

Subsequent studies assessed the impact of diarrhoea on the growth of large groups of children. The contribution of diarrhoea to growth failure in children in developing countries was estimated to be as high as 25–30%. The same effect is, however, not seen in children in developed countries. This lack of effect may be due to the lower burden of disease in developed countries, the better nutrition of children in these countries, and bias in measuring episodes of morbidity.[3]

Martorell[3] measured growth and episodes of infection in children in eastern Guatemala from shortly after birth to seven years. Diarrhoea was associated with reduced growth rate while there was no significant association between fever or respiratory illness and growth. Children with a low prevalence of diarrhoea (less than or equal to 5% of time with diarrhoea) grew 6,3% more in length and

11% more in weight than those with a high prevalence of diarrhoea (more than 5% of time with diarrhoea). This effect occurred independently of the type of nutritional supplement that the children were receiving (some were on a high and others on a low energy supplement).

Diarrhoea had a similar effect on the growth of children in The Gambia. Rowland[4] found that there was a negative correlation between weight and height gain and diarrhoea prevalence in children younger than three years. Malaria was the only other disease for which there was also a significant association in this study. The regression coefficient for the diarrhoea versus weight gain was -95+/- 8,5 g/kg body weight per month.

A more recent study from northern Brazil[5] analysed surveillance data collected between August 1989 and December 1998. The number of episodes of diarrhoea, days of diarrhoea and episodes of persistent diarrhoea (longer than 14 days), helminth infections and height-for-age Z-score were reported. There was a inverse relationship between the number of episodes of diarrhoea and growth: an average burden of diarrhoea of 9,1 episodes of diarrhoea before two years was associated with a 3,6 cm decrease in longitudinal growth at age seven years. There was also a negative association between intestinal helminth infections and height for age Z-score. These associations remained significant after controlling for nutrition during infancy, other parasitic infections, diarrhoea in later childhood, and socioeconomic status.

Checkley and co-workers[6] performed a multi-country analysis of the effect of diarrhoea on childhood stunting. Nine studies performed in South America, Africa, and Bangladesh between 1978 and 1998 were included. After correction for socioeconomic status, the odds of stunting by 24 months increased with every episode of diarrhoea and with each day of diarrhoea. Using pooled data, the proportion of stunting that could be attributed to more than or equal to five episodes of diarrhoea was 25% and for having diarrhoea more than or equal to 2% of the first 24 months of life was 18%.

The preceding data suggests that reducing the incidence and prevalence of diarrhoea in children in developing countries will lead to a reduction in malnutrition. This conclusion has been challenged by studies from Bangladesh, The Gambia, and Egypt.

Briend[7] challenged the importance of diarrhoea as a cause of malnutrition in communities. This challenge was based on concerns that there was inadequate epidemiological evidence to support causality. Briefly, the concerns were related to: temporal ambiguity; lack of consistency between short and long term studies (in terms of magnitude); poor strength of association; inadequate evidence for biological plausibility; and lack of evidence of a sustained effect of diarrhoea. A few epidemiological studies seem to support this position.

Poskitt and co-workers[8] reviewed data collected from 1979 through 1993 in The Gambia. Clinic visits for diarrhoea and growth parameters of 1190 children aged 0–2 years were analysed. During the study period the number of clinic visits for diarrhoea decreased. There was, however, no improvement in weight gain or longitudinal growth in this period.

A longitudinal study from Egypt[9] found that diarrhoea was unlikely to have a major impact on the prevalence of malnutrition. Diarrhoea was associated with a small increase in the risk of low height-for-age and children showed some catch-up growth in the following observation period. There was no effect on the weight-for-age or weight-for-height. On the other hand, children with a low weight for height (as well as those with poor sanitation and previous episodes of diarrhoea) had an increased risk of diarrhoea. Few children in this study however had persistent diarrhoea (1%) and the prevalence of malnutrition in this population was lower than in other populations that have been studied. The results of this study may thus not be applicable to poorer populations.

Although no organism has consistently been identified as a cause of persistent diarrhoea, in certain geographic areas entero-aggregative *E. coli,* cryptosporidium, and giardia lamblia have been identified as important causes of persistent diarrhoea and malnutrition. In a Peruvian study[10] children infected with cryptosporidium had faltering both in weight and height gain for months after the initial infection. Stunted children and infants younger than six months did not have catch-up growth during the study period. In HIV infected children cryptosporidium infection was especially severe, often causing severe malnutrition, monosaccharide intolerance, and death.

Pathophysiology

Many factors contribute to the detrimental effect of diarrhoea on nutritional status. Reduced intake (due to anorexia, vomiting, and with-holding of feeds), maldigestion, malabsorption, increased nutrient losses, and the effects of the inflammatory response are some of the factors involved.

Intake

Childhood infections are frequently associated with reduced dietary intake. This effect is most prominent in children with diarrhoea. A study from Gautemala[11] has found that diarrhoea was associated with a reduction of daily dietary intake of 160 calories and 3 g of protein for children between the ages of 12 and 60 months. The reduction in children with respiratory infections was considerably less (67 calories and 1 g of protein per day). Other studies from Costa Rica, Guatemala, Bangladesh and Uganda also found significant reductions in dietary intake in children with diarrhoea.

Absorption and digestion

Acute diarrhoea causes increased losses of fluid and electrolytes. These are accompanied by varying degrees of nutrient maldigestion, malabsorption and losses. Children with high stool losses have significant malabsorption of protein, carbohydrates, and fat. Additionally, enteric protein losses are often increased. Studies of children with acute and persistent diarrhoea in developing countries have increased our knowledge of these effects.

High volume stool losses (greater than 30 ml/kg/day) are associated with a negative balance for protein, fat, and sugar absorption. Balance studies conducted in Cape Town[12] found that increasing volumes of stool losses lead to decreasing nutrient absorption. Once stool volume exceeded 30–50 g/kg/day, children were unable to achieve a positive nutrient balance with normal infant formula. Apparent nitrogen absorption decreased by 0,86% and apparent fat absorption 0,4% for each gram increase in stool weight. A stool weight of 50 g/kg/day led to an apparent nitrogen absorption of 59% and fat absorption of 52 %. Sugar malabsorption also increased with increasing stool losses. In these studies the effect was less in children receiving a soya based formula.

Enteric infections often cause increased loss of endogenous proteins, particularly after invasive bacterial infections. Hoffman[13] measured alpha-1-antitrypsin in stool of infants with diarrhoea in Cape Town; losses were increased in children with enteric infections. Other studies have similarly documented increased protein loss during infectious diarrhoea[14] and after measles.[15]

Inflammatory response

The inflammatory response that accompanies enteric infections contributes to the detrimental effects of diarrhoea on nutritional status. Energy requirements are increased, appetite is suppressed by cytokine release, and catabolism and loss of nutrients is accelerated.

Various markers of inflammation (e.g. CRP, IL6, IL8, and TNF-α) are increased in diarrhoea:

1. Entero-aggregative *E. coli* infection, an important cause of both acute and persistent diarrhoea in developing countries, leads to a pronounced increase in IL8.[16]
2. Serum CRP is higher in children with bacterial than viral diarrhoea: a Taiwanese study[17] found that CRP as well as IL6 and IL8 were more elevated in children with bacterial than those with viral diarrhoea. Rotavirus, however, also caused a significant systemic inflammatory response.
3. Bacteraemia, a severe complication of diarrhoea in children, is also associated with a systemic inflammatory response.[18]
4. Cytokine activation (CRP, IL6, interferon (IFN)-gamma) in HIV infected patients predicts poor survival.[19]

HIV, intestinal disease and malnutrition

Diarrhoea and malabsorption are important complications of HIV infection that contribute to the high morbidity and mortality. Episodes of diarrhoea are often complicated by severe malabsorption.

Lactose malabsorption is a common complication in young HIV-infected children with diarrhoeal disease.[14,20,21] Thirty to sixty percent of these children have evidence of lactose malabsorption. In the presence of persistent diarrhoeal disease, it is advisable to use low lactose feeds. In the absence of diarrhoea however lactose-containing feeds are usually tolerated.

Fat malabsorption is also detected in up to 30% of children with HIV infection.[22] Exocrine pancreatic insufficiency[23,24,25] and mucosal factors contribute to the steatorrhoea. Despite the high proportion of children with increased faecal fat there is presently no clear association with malnutrition. At this stage, it seems prudent to provide pancreatic enzyme supplementation to HIV infected children with documented or suspected exocrine pancreatic insufficiency.

Management

Initially the major emphasis of treatment of acute diarrhoea in children is the prevention and treatment of dehydration, electrolyte abnormalities and comorbid conditions (e.g. pneumonia, bacteraemia). Nutritional management is, however, not delayed and is an integral part of their management. Objectives are to prevent weight loss, to encourage catch-up growth during recovery, to shorten the duration and to decrease the impact of the diarrhoea on the child's health.

Feeds are only interrupted for a few hours to allow correction of severe dehydration and shock.[26] There is no indication for "regrading" of feeds in infants. Giving diluted or low volumes of feeds aggravates the weight loss that follows an episode of diarrhoea and does not reduce the duration or severity of the diarrhoea significantly. Breastfeeding should not be interrupted; it shortens the duration of the diarrhoea and improves energy intake.

Initially children continue with their normal feeds and specialised formulae are indicated for those with malabsorption. Lactose free formulae are given to children with suspected lactose intolerance; this occurs more frequently in malnourished children and those whose diarrhoea persists longer than 3–4 days. Hydrolysed infant formulae are used for those with suspected protein sensitive enteropathy and may be of value in some children with severe malnutrition or HIV infection.[27]

Zinc

Zinc, a cofactor for many enzymes and required for cell division, has a number of potentially beneficial effects on the intestine. It reduces intestinal permeability in malnourished children with diarrhoea[28,29] and, in animal models, tight junction morphology is improved and paracellular permeability decreases after zinc supplementation.[30]

Clinical benefits of zinc supplementation include reduction of the severity and duration of diarrhoea in children at high risk of zinc deficiency. A recent meta-analysis[31] of randomised, placebo controlled trials of zinc supplementation in children with diarrhoea found that zinc supplementation reduced the duration of acute diarrhoea by 15% and the duration of persistent diarrhoea by 15,5%. Duration of diarrhoea was also reduced by 18,8% and 12,5% for acute and persistent diarrhoea respectively. Weight and length gain is also improved in children after zinc supplementation. A more recent South African study,[32] however, did not find the same benefit in children with diarrhoea. The implication for clinical practice in South Africa still needs to be determined.

Vitamin A

Studies from developing countries have found that vitamin A supplementation reduces the number of episodes of severe diarrhoea and diarrhoeal disease deaths in children. However, there is less evidence that vitamin supplementation will benefit children once they have diarrhoea. Supplementation with vitamin A also reduces intestinal permeability in children in developing countries supporting the role of vitamin A in maintaining the intestinal barrier function.[33,34]

Novel Agents

The role of glutamine and its derivatives and arginine in the management of acute infectious diarrhoea are not well established. These agents promote mucosal recovery and may accelerate recovery from diarrhoea.

Conclusions

The detrimental effects of diarrhoea, in particular persistent diarrhoea, on the nutrition of individual children are well recognised. The effects of diarrhoea on the prevalence of malnutrition in a population, however, are complex. Addressing only diarrhoea or only food security is unlikely to be successful in decreasing the prevalence of malnutrition. Existing evidence provides some guidelines as to the optimal nutritional management of children with diarrhoea and novel treatments may prove to be valuable in future.

References

1. Scrimshaw NS, Taylor CE, Gordon JE. Interactions of nutrition and infection. Monogr Ser World Health Organ. 1968;57:3–329.
2. Mata LJ, Urrutia JJ, Lechtig A. Infection and nutrition of children of a low socioeconomic rural community. Am J Clin Nutr. 1971;24:249–59.
3. Martorell R, Habicht JP, Yarbrough C, Lechtig A, Klein RE, Western KA. Acute morbidity and physical growth in rural Guatemalan children. Am J Dis Child. 1975;129:1296–1301.
4. Rowland MG, Cole TJ, Whitehead RG. A quantitative study into the role of infection in determining nutritional status in Gambian village children. Br J Nutr. 1977;37:441–50.
5. Moore SR, Lima AA, Conaway MR, Schorling JB, Soares AM, Guerrant RL. Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering. Int J Epidemiol. 2001;30:1457–64.
6. Checkley W, Buckley G, Gilman RH, et al. Multi-country analysis of the effects of diarrhoea on childhood stunting. Int J Epidemiol. 2008;37:816–30.
7. Briend A. Is diarrhoea a major cause of malnutrition among the under-fives in developing countries? A review of available evidence. Eur J Clin Nutr. 1990;44:611–28.
8. Poskitt EM, Cole TJ, Whitehead RG. Less diarrhoea but no change in growth: 15 years' data from three Gambian villages. Arch Dis Child. 1999;80:115–9; discussion 119–20.
9. Wierzba TF, El-Yazeed RA, Savarino SJ, et al. The interrelationship of malnutrition and diarrhea in a periurban area outside Alexandria, Egypt. J Pediatr Gastroenterol Nutr. 2001;32:189–96.
10. Checkley W, Epstein LD, Gilman RH, Black RE, Cabrera L, Sterling CR. Effects of Cryptosporidium parvum infection in Peruvian children: growth faltering and subsequent catch-up growth. Am J Epidemiol. 1998;148:497–506.
11. Martorell R, Yarbrough C. The Energy Cost of Diarrheal Diseases and Other Common Illnesses in Children. In: N S Scrimshaw L C Chen, ed. Diarrhea and Malnutrition. New York and London: Plenum Press; 1983:125–141.
12. Mann MD, Hill ID, Bowie MD. Absorption and retention in acute diarrhoea. Eur J Clin Nutr. 1990;44:629–35.
13. Hoffman HD, Hanekom C. Random faecal alpha-1-antitrypsin excretion in children with acute diarrhoea. J Trop Pediatr. 1987;33:299–301.
14. Zuin G, Fontana M, Nicoli S, Scapellato L, Tamburini G, Gaboardi F. Persistence of protein loss in acute diarrhoea. A follow-up study by faecal alpha-1-antitrypsin measurement. Acta Paediatr Scand. 1991;80:961–3.
15. Sarker SA, Wahed MA, Rahaman MM, Alam AN, Islam A, Jahan F. Persistent protein losing enteropathy in post measles diarrhoea. Arch Dis Child. 1986;61:739–43.
16. Khan K, Konar M, Goyal A, Ghosh S. Enteroaggregative Escherichia coli infection induces IL-8 production via activation of mitogen-activated protein kinases and the transcription factors NF-kappaB and AP-1 in INT-407 cells. Mol Cell Biochem. 2009.
17. Yeung C, Lee H, Lin S, et al. Serum cytokines in differentiating between viral and bacterial enterocolitis. Ann Trop Paediatr. 2004;24:337–43.
18. Korczowski B, Szybist W. Serum procalcitonin and C-reactive protein in children with diarrhoea of various aetiologies. Acta Paediatr. 2004;93:169–73.
19. Zulu I, Hassan G, Njobvu R. N L, Dhaliwal W, Sianongo S, Kelly P. Cytokine activation is predictive of mortality in Zambian patients with AIDS-related diarrhoea. BMC Infect Dis. 2008;8:156.
20. Yolken RH, Hart W, Oung I, Shiff C, Greenson J, Perman JA. Gastrointestinal dysfunction and disaccharide intolerance in children infected with human immunodeficiency virus. J Pediatr. 1991;118:359–63.
21. Miller TL, Orav EJ, Martin SR, Cooper ER, McIntosh K, Winter HS. Malnutrition and carbohydrate malabsorption in children with vertically transmitted human immunodeficiency virus 1 infection. Gastroenterology. 1991;100:1296–302.
22. Intestinal malabsorption of HIV-infected children: relationship to diarrhoea, failure to thrive, enteric micro-organisms and immune impairment. The Italian Paediatric Intestinal/HIV Study Group. AIDS. 1993;7:1435–40.
23. Carroccio A, Fontana M, Spagnuolo MI, et al. Pancreatic dysfunction and its association with fat malabsorption in HIV infected children. Gut. 1998;43:558–63.
24. Carroccio A, Fontana M, Spagnuolo MI, et al. Serum pancreatic enzymes in human immunodeficiency virus-infected children. A collaborative study of the Italian Society of Pediatric Gastroenterology and Hepatology. Scand J Gastroenterol. 1998;33:998–1001.
25. Carroccio A, Di Prima L, Di Grigoli C, et al. Exocrine pancreatic function and fat malabsorption in human immunodeficiency virus-infected patients. Scand J Gastroenterol. 1999;34:729–34.
26. Guarino A, Albano F, Ashkenazi S, et al. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: executive summary. J Pediatr Gastroenterol Nutr. 2008;46:619–21.
27. Amadi B, Mwiya M, Chomba E, et al. Improved nutritional recovery on an elemental diet in Zambian children with persistent diarrhoea and malnutrition. J Trop Pediatr. 2005;51:5–10.
28. Roy SK, Behrens RH, Haider R, et al. Impact of zinc supplementation on intestinal permeability in Bangladeshi children with acute diarrhoea and persistent diarrhoea syndrome. J Pediatr Gastroenterol Nutr. 1992;15:289–96.
29. Alam AN, Sarker SA, Wahed MA, Khatun M, Rahaman MM. Enteric protein loss and intestinal permeability changes in children during acute shigellosis and after recovery: effect of zinc supplementation. Gut. 1994;35:1707–11.
30. Rodriguez P, Darmon N, Chappuis P, et al. Intestinal paracellular permeability during malnutrition in guinea pigs: effect of high dietary zinc. Gut. 1996;39:416–22.
31. Lukacik M, Thomas RL, Aranda JV. A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea. Pediatrics. 2008;121:326–36.
32. Luabeya KA, Mpontshane N, Mackay M, et al. Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South african children: a randomized controlled trial. PLoS One. 2007;2:e541.
33. Chen P, Soares AM, Lima AAM, et al. Association of vitamin A and zinc status with altered intestinal permeability: analyses of cohort data from northeastern Brazil. J Health Popul Nutr. 2003;21:309–15.
34. Vieira MM, Paik J, Blaner WS, et al. Carotenoids, retinol, and intestinal barrier function in children from northeastern Brazil. J Pediatr Gastroenterol Nutr. 2008;47:652–9.

Nutrition in children posttransplantation

Goddard EA
Department of Paediatrics, Paediatric Gastroenterology, Red Cross Children's Hospital, Rondebosch, Cape Town
Correspondence to: Dr EA Goddard, e-mail: liz.goddard@uct.ac.za

Abstract

Nutrition support is a vitally important issue in the pretransplantation period. Once a child has been assessed and placed on a list for transplantation the child must see a dietitian to optimise the child's nutritional status as this is vital to improve the outcome at surgery. Children with chronic liver disease who are candidates for transplantation have a better posttransplant outcome and growth potential if their nutrition is optimised pretransplantation. Well monitored nutritional support posttransplantation improves the long-term quality of life by minimising the complications associated with transplantation. An interdisciplinary approach to nutritional care of a transplant recipient involving the expertise of paediatricians, surgeons, dietitians and nursing staff is essential to optimise the outcome of these patients.

S Afr J Clin Nutr 2010;23(1) Supplement:S19-S21

Introduction

Transplantation in children differs in some aspects of perioperative and posttransplant care from adult transplantation because of differences in the aetiology of the primary underlying disease, patient size, immunologic responsiveness, medication pharmokinetics as well as growth and development issues.

There is little data looking at nutrition posttransplantation in children. Improvement in growth should occur postoperatively. Factors associated with continued poor growth include age at transplantation, malnutrition, surgical complications of the transplant, allograft dysfunction and excessive corticosteroid use.

The nutritional goal in the immediate postoperative period is to provide adequate nutrition to "catch up" the pretransplant nutritional deficit associated with a chronic liver disease and to allow for recovery from major surgery.

Early oral or enteral feeding should be strived for after successful uncomplicated heart, liver and kidney transplantation. Aggressive early posttransplant nutritional therapy facilitates wound healing, decreases infectious complications and shortens ventilation time. Parenteral nutrition is needed if there is prolonged postoperative ileus or if gastrointestinal complications of surgery limit enteral feeding.

All transplant patients require nutritional follow up to assess nutritional status and to detect, prevent and treat late-onset complications such as obesity, hyperglycaemic hyperlipidaemia or osteoporosis. Dietetic support is an essential component of the transplant team. Although this manuscript focuses on the nutritional care of the paediatric patient post liver transplantation, most aspects of the management is relevant to a patient undergoing any solid organ transplant. Aspects of care specific to renal or intestinal transplantation will also be addressed.

LIVER

Children with chronic liver disease (CLD) are at high risk for malnutrition, especially when the disease is cholestatic in nature and its onset is in infancy. The most common CLD in our setting requiring transplantation in childhood is biliary atresia (70% of cases). Malnutrition is a manifestation of decompensated liver disease. Liver transplantation is a complex procedure that is performed in children who often have multiple co-morbidities.

Growth retardation and malnutrition are common complications of CLD because of decreased intake, malabsorption and relative growth hormone resistance. Nutritional support is complicated by increased energy expenditure, malabsorption secondary to gut oedema, cholestasis and poor intake. Cholestasis leads to malabsorption of fat soluble vitamins. Managing malnutrition in children in with end stage liver disease is a challenge.

Pretransplant nutritional therapy

In children with end-stage liver disease (ESLD) the nutritional goal is to maintain maximum growth potential, prevent further liver injury, promote liver regeneration, minimise risk of infection and avoid vitamin and mineral deficiencies.[1] They require 130–150% of the recommended dietary allowances (RDA) of energy for their ideal body weight. About 60–70% of the energy should be given as high complex and simple carbohydrates. The later should be limited when glucose intolerance is present. The other 30–40% of energy are provided by fat with some as medium chain triglycerides, if fat malabsorption is present. Long chain triglycerides should not be decreased to less than 10% of the total energy intake to prevent deficiencies in essential fatty acids. The RDA of protein for children with CLD is 2.5–3.0 g/Kg of ideal body weight because of their catabolic state and the need to improve growth rate.[2] Branched chain amino acids (BCAA) (leucine, isoleucine and valine) improve

hepatic protein synthesis. Most formulas contain between 16–53% BCAA. If the patient is encephalopathic the protein may need to be decreased (1.0–1.5g/Kg) and the more expensive formulas with a high content of BCAA may be considered.

Nasogastric tube feeds may be required in children with advanced liver disease who are unable to take sufficient feeds orally. If continuous nasogastric feeds become necessary it is important to continue small amounts of oral feeds so that the infants do not lose feeding skills after transplantation.

Patients awaiting orthotopic liver transplantations should take a daily multivitamin, as well as fat soluble vitamin supplementation including additional vitamin D as needed together with folic acid, zinc and magnesium.

Posttransplant nutritional therapy

Early postoperative period

The nutritional goal in the immediate postoperative period (two months) is to provide adequate nutrition to correct the pretransplant nutritional deficit associated with chronic liver disease and to allow for the additional stress of major abdominal surgery.

Preoperative malnutrition, stress of the surgical procedure, immunosuppressive therapy, liver or kidney dysfunction or sepsis are all factors that contribute to a persistent catabolic state in the early posttransplant period.

Early use (within the first 24–36 hours) of enteral feeding is recommended post an uncomplicated liver transplant, once the postoperative ileus has resolved.[3] This is usually done using continuous nasogastric feeding of a polymeric feed. If this is not tolerated then use of a semi-elemental feed would be considered. When the patient begins to eat solid food, enteral feeding can be used as overnight feeds to enhance the appetite during the day. The oral intake can be changed to a regular diet as tolerated, and once there is adequate oral intake the enteral feeds can be stopped. In this period the patients have a high protein, high energy diet to counteract the weight loss associated with pretransplant cachexia. Patients are often not advised when to wean off this diet. Parental nutrition is needed if there is a prolonged postoperative ileus or gastrointestinal complications. Chylous ascites may be related to lymphatic disruption and responds to fat restricted diet.

Although liver transplantation allows resolution of metabolic dysfunction PEM and nutritional deficiencies, the need for nutrition monitoring and therapy continues. Patients who are not malnourished and who can eat within a few days of the transplant may not need post-op nutrition support.

Metabolic/electrolytes

Routine posttransplant care includes monitoring fluid balance carefully with strict intake and output measurements and daily body weight measurements. Many laboratory tests are monitored which include full blood count, differential and clotting, blood glucose, electrolytes, calcium, phosphorus, magnesium, albumin and liver enzymes. Electrolyte abnormalities are common in the early posttransplant period. Sodium can be lost in the urine, nasogastric tube losses, and abdominal drains. Serum potassium, phosphate and magnesium levels can deplete early post liver transplant due to the use of diuretics and the refeeding syndrome. Cyclosporin, tacrolimus and kidney insufficiency can cause hyperkalaemia. Cyclosporin can accelerate magnesium losses.

All children routinely receive multivitamin supplements. In the long term the transplant recipient should only receive dietary supplements, if indicated.

Long-term posttransplant nutritional therapy

The diet of the liver transplant recipient should be monitored for energy and protein intakes for the first 2–3 years posttransplantation to maximise growth and to prevent obesity and its complications.

Obesity

A major problem in the transplant recipient is long-term excess energy and fat intake with excessive weight gain leading to overweight and obesity. The side effects most often seen with over-nutrition would include hypertension, diabetes mellitus and altered blood lipids. Once the pretransplant loss of weight and muscle has been regained there must be careful nutritional monitoring to prevent excessive weight gain. Weight gain is most dramatic between two and 16 months after transplantation. In a study of adult liver recipients, 43% were obese 18 months after transplant and a further 24% were overweight.[4] The causes of weight gain are multifactorial, the appetite is definitely stimulated by corticosteroids and often the patients are quite sedentary.

Patients and their families need to be educated about posttransplant obesity and its risks. It is important to monitor weight gain and to make aggressive efforts to decrease high fat foods for children who are gaining weight excessively. Most of the weight gained after transplantation is fat. Muscle mass is not always regained. A diet low in saturated fat and high in fibre and vegetables together with regular aerobic and weight bearing exercise has been shown to have a major role in preventing weight gain and lowering lipid levels posttransplant. Dietary support by the dietitian is crucial.

Growth retardation

Many children, particularly those with cholestatic disease, have growth retardation before liver transplantation, because of decreased intake, malabsorption and relative growth hormone resistance. Generally transplanted children do not have complete catch up growth and achieve a final height below their genetic potential.[5,6] A recent study found that after liver transplantation in childhood, 50% of patients reached a final height lower than -1.3SD of their genetic potential.[5] Ng et al found that 73% of recipients were below average height five years post liver transplantation.[6] The growth delay in children after transplantation is often attributed to corticosteroid use but this is not the only factor. However, excessive corticosteroid use must be avoided.

Diabetes mellitus

The occurrence of diabetes mellitus (DM) in transplant recipients is significantly increased when compared with the general population. The real incidence in posttransplant DM in children is unknown. In small retrospective studies it is reported to be between two and 24%.[7] In an audit at Red Cross Children's Hospital the incidence in liver and kidney transplants was 6%. The high risk factors in our group were black patients (50%), tacrolimus, high dose steroids and overweight. Many children can be weaned off insulin during follow up.

Table I: Side effects of immunosuppressive agents

Corticosteroids:
Growth retardation
Increased susceptibility to infection
Impaired wound healing
Cataracts
Glucose intolerance
Hypertension
Cushingoid facies and acne
Mycophenolate mofetil:
Gastrointestinal disturbances
Nausea and vomiting
Diarrhoea
Calcineurin Inhibitors (Ccyclosporine and tacrolimus)
Cyclosporine
Nephrotoxicity
Hypertension
Gum hyperplasia/hypertrichosis
Hyperkalaemia
Hypomagnesaemia
Hyperlipidaemia
Tacrolimus
Hyperkalaemia
Hypomagnesaemia
Diabetes mellitus
Diarrhoea and abdominal pain
TOR inhibitors (sirolimus)
Hyperlipidaemia
Delayed wound healing

* Nutritional side effects are in bold

Table II: Medications that alter calcineurin (CNI) levels

Medications that decrease CNI levels:
Anticonvulsants
- Barbiturates
- Phenytoin
- Carbamazepine
Rifampin
St John's wort
Medications that increase CNI levels:
Calcium-channel blockers
- Verapamil
- Diltiazem
- Nicardipine
- Amlodipine
Azole antifungals
- Fluconazole
- Ketoconazole
Macrolide antibiotics
- Erythromcycin
- NOT azithromycin
Corticosteroids
Somatostatin
Amiodarone
Grapefruit juice
Medications that increase renal toxicity:
Vancomycin
Aminoglycosides
Bactrim
Aciclovir
Ganciclovir
Amphotericin

New onset diabetes mellitus is a known side effect of both glucocorticosteroids and the calcineurin inhibitors because these drugs affect insulin secretion and tissue sensitivity or resistance to the effects of insulin. Age, family history, African ethnicity and use of tacrolimus are all risk factors for a higher incidence of diabetes in transplant patients.

Metabolic bone disease

The adverse effects on bone that occur posttransplantation include osteoporosis/bone loss, fractures and avascular necrosis. Most liver transplant recipients lose bone mass for 3–6 months after transplantation. In patients with a normally functioning graft this bone loss stops after six months.[1] Adequate treatment with calcium and vitamin D in the pre- and posttransplantation periods along with physical activity is important to decrease the complications of metabolic bone disease.

Immunosuppression

Most paediatric liver transplant recipients are initially treated with a triple immmunosuppression regimen. The side effects of the more common immunosuppressive agents (Table I) together with the more common drugs and foods that affect the levels of the calcineurin inhibitors (cyclosporine and tacrolimus) (Table II) should always be brought in mind.

RENAL

Meticulous fluid and electrolyte management is important in the paediatric renal transplant patient because such patients often need additional intravascular volume repletion in the perioperative period to establish diuresis and avoid delayed graft function. This is critical if a small child has received an adult graft.

There is little data on dietary recommendations for children following renal transplantation. Energy and protein needs are increased immediately after transplant. Protein needs are 150–200% of the recommended daily allowance (RDA) for age and weight. It is important to meet these needs to achieve wound healing to help prevent muscle wasting associated with high dose steroids. Supplemental enteral or parenteral nutrition is indicated in patients who cannot meet their energy and nutrient requirements via oral intake in the first few days posttransplant.

INTESTINAL

The outcome after intestinal transplantation has improved over the past decade. The postoperative management after liver transplantation is the most challenging of all the solid organ transplants. Total parenteral nutrition (TPN) is required for the first 3–6 weeks after transplantation. Continuous small volume (2 to 5 ml/hr) of enteral feeding is usually started within 10 days of the transplant. Elemental enteral formulae are used. The choice of enteral diet depends on age, previous diets and previous sensitisations. Posttransplant fat malabsorption can occur secondary to the severance of lymphatic channels of the intestinal graft.[8]

Once enteral feeding is established, the TPN is decreased. TPN is usually maintained until 70% of nutritional requirements are tolerated enterally. When the child is stable and tolerating enteral feeds, solid food is introduced according to the child's age and preference. Chronically ill infants and children who are at risk for oral aversion enteral tube feeding is necessary for many months. The transition to full oral intake may take years and in some cases is never achieved. Development of food allergies is common so initial avoidance of milk and eggs from the diet is recommended.

References

1. Ramaccioni V, Soriano H E, Arumugam R, et al. Nutritional Aspects of Chronic Liver Disease and Liver Tranplantation in Children. J Pediatr Gastroenterol Nutr. 2000;30:361–367
2. Campos ACL, Matias JEF and Coelho JCU. Nutritional Aspects of Liver Transplantation. Curr Opinion in Clin Nutr and Metabolic Care. 2002;5:297–307
3. Weiman A, Ebener Ch, Holland-Cunz S, et al. Surgery and Transplantation – Guidelines on Parenteral Nutrition. Chp 18. German medical Science 2009;7:1–15.
4. Munoz S, Deems R, Moritz M, et al. Hyperlipidaemia and Obesity after Orthotopic Liver Transplantation. Transplantation Proc. 1991;23(1):1480–1483
5. Scheenstra R, Jan Gever W, Odink RJ, et al. Growth and Final Height after Liver Transplantation. J Pediatr Gastroenterol Nutr. 2008;47:165–171
6. Ng VL, Fecteau A, Shepherd R, et al. Outcomes of 5-Year Survivors of Pediatrric Liver Transplantation: Report on 461 Children from a North American Multicenter Registry. Pediatrics 2008;122;e1128-e1135
7. Gokce S, Durmaz O, Coskun C, et al. Investigation of impaired carbohydrate metabolism in pediatric liver transplant recipients. Pediatr Transplant 2009;13:873–880
8. Encinas JL, Luis A, Avila LF, et al. Nutritional Status After Intestinal Transplantation in Children. Eur J Pediatr Surg 2006;16:403–406.

Management of severe malnutrition

Schubl C
Division of Human Nutrition, Tygerberg Academic Hospital and Stellenbosch University; Tygerberg, South Africa
Correspondence to: Ms C Schubl, e-mail: cschubl@pgwc.gov.za

Abstract

In summary, if the Millenium Development Goals (MDGs) are to be addressed effectively, it is imperative that severe malnutrition be addressed at the international and national level, using strategies that work, and that additional resources are committed to improving hospital treatment and establishing community-based rehabilitation programmes.[20] Many gaps still exist in our knowledge regarding the management of severe malnutrition at all levels. Until such time when research can fill these gaps, we will have to continue to use what guidelines have shown to produce positive results.

S Afr J Clin Nutr 2010;23(1) Supplement:S22-S24

Severe malnutrition is defined as a severe wasting (< 70% weight for length or < -3 Z-score) and/or oedema.[1] The global estimate of wasting is approximately 10% (approx 55 million children), with severe wasting at 3,5% (approximately 19 million children).[2] Stunting, however, is regarded as a problem of greater magnitude than underweight or wasting, as it more accurately reflects nutritional deficiencies and illness that occur during the most critical period of development and growth.[3] Twenty four countries account for more than 80% of the worldwide burden of chronic undernutrition (i.e. stunting). South Africa is counted amongst one of these countries.[3] It is not surprising that stunting is highest for the poorest segments of the population within countries.[2] Stunting affects approximately 195 million children under the age of five years.[3] Malnutrition is an underlying factor in approximately 50% of the nearly 10 million deaths in children under the age of five years from preventable causes.[4]

Serious attention needs to be paid to the long-term effects and burden of undernutrition. The child is at its most vulnerable during the period of most rapid growth and development (this includes the period of significant brain formation).[2,3] Chronic undernutrition results in diminished cognitive and physical development.[3] Early growth failure (within the first two years of life) is associated with reduced adult stature, which in turn is associated with lower educational achievement as well as lower economic status in adulthood through reduced productivity and income earning capacity.[3,5] The situation is further exacerbated by the increased risk of chronic disease in adulthood in children who had deficient growth before the age of two years, but experienced rapid weight gain in later stages of childhood.[3]

Globally, progress toward achieving the Millenium Development Goals (MDG) has been varied, with some countries, most of them in sub-Saharan Africa, actually worsening in terms of the numbers of children who are underweight. The stunting prevalence has not decreased in the sub-Saharan Africa since the mid-1990s, with South Africa being one of these countries according to UNICEF.[6,7] Furthermore, South Africa has shown an increased trend since 1990 in the mortality of children under the age of 5 years.[8]

There is, however, difference in the statistics given by UNICEF and the National Food Consumption Survey. From the NFCS there appears to be a slight decline in stunting from 1994 to 2005 at 23% and 18 % respectively. In the Western Cape stunting has remained static at around 12%. However, it would appear that the prevalence of wasting over the same period has increased slightly from 3 to 4,5 nationally and alarmingly from 1 to 11,5 % in the Western Cape in the period from 1994 to 2005.[9]

Annually large amounts of money are invested to improve nutritional outcomes in poor countries by the international community. Approximately $250–300 million a year for the first half of this decade was invested in basic nutrition. This, however, translates to just over $2 a year per infant for the 130 million infants under two years who could benefit from the investment. This is less than the estimated $5–10 per child which effective large scale community nutrition programmes should be spending. Interestingly HIV/AIDS receives $2.2 billion per year in foreign aid, although it contributes less to "disability adjusted life years" than does child undernutrition. The serious consequences of undernutrition are not well understood at "high level".[7]

National policies

To achieve the first MDG target depends to a great extent on the effective implementation of large scale nutrition and health programmes that will provide appropriate food, health and care for all children within a country.[3]

The Lancet series[10] reviewed the national strategies that have been proven to work. The interventions that had the greatest impact on reducing malnutrition and mortality were: iron supplementation, salt iodisation, vitamin A supplementation for children aged 6–59

months, breastfeeding strategies based on individual and group counselling, zinc supplementation in the management of diarrhoea, fortification of staple foods, behaviour change, communication to improve complementary feeding and interventions to improve hygiene practices.[3,10]

Certain actions have been found to be ineffective in reducing undernutriton such as growth monitoring (unless it is linked to adequate nutrition counselling and referral), preschool feeding programmes targeting children older than 24 months of age and school feeding programmes targeting children older than five years of age. This last strategy may, however, have non-nutritional benefits for education.[10]

Though not all effective strategies can be generalised for all countries, a sizeable effect can be achieved with high coverage of four or five proven interventions.[11] However, for national strategies to be effective, commitment is required from all the country's role-players. In spite of the dire statistics, nutrition remains a low priority on the national development agendas of many countries and often has no clear institutional home.[3,11]

Undernutrition often remains unnoticed until it has reached a severe level. Children may appear healthy even whilst facing the grave risks associated with undernutrition. Policy makers often do not understand the urgency of the situation and may not understand how improved nutrition contributes to long-term national, social and economic goals.[3]

In many cases, national programmes do not fully succeed due to the lack of political commitment (defined as the allocation of human, financial and organisational resources).[11] National leaders and those who control national financial resources are more likely to be more successful in promoting nutrition strategies than public health advocates or technical staff from donor or UN agencies. Nutrition goals therefore should be included in all appropriate government sectors and their policies and operations. National sectors, other than Health, may also have an impact on nutritional status e.g. economic policies to address poverty, trade and agriculture, opportunities that are often under-exploited.[11]

However, political commitment to nutrition will also only result in improvements in nutritional status if supported by interventions that are effective and that are able to be implemented at high and sustainable levels of coverage. Historical evidence has shown that the nutrition of mothers and children can be improved relatively quickly, given the combined effort politically, strategic planning and adequate resources.[11]

Paradoxically, South Africa has poor health outputs and outcomes despite relatively high health expenditure and many supportive policies. The poor successes of policies are often due to the failure to build capacity to implement the policies and programmes and to monitor implementation. A great deal of attention and resources (including medical personnel) have been absorbed by a few health programmes, e.g. HIV programmes. South Africa's commitment to the MDGs is being crippled by the relentless rise in the burden of diseases which is leading to a vicious cycle of increased expenditure, distorted responses by the health system, out-migration of human resources and increased social issues.[12]

The difficulties in implementing effective national strategies successfully is further exacerbated by an international nutrition system that has little respect for country generated plans, local timetables or political processes of a country.[11]

International actions

International initiatives often do not have the desired effects as they often behave adversarially and compete for attention. They also often siphon off scarce human resources and promote poorly designed solutions to problems that they cannot solve on their own. The function of international initiatives should be to directly support national structures in high burden countries and to produce "global public goods" e.g. setting standards and identifying priorities; mobilising, pooling and distributing financial resources; providing nutrition services where national sectors are unable or unwilling to do so themselves; strengthening human and institutional resources through training and capacity building and finally research and development.[7]

The international community devotes few resources to nutrition-related organisational development in low and middle income countries. Many of the major international organisations seem to lack appropriately skilled staff at central level.

Efforts to manage undernutrition internationally have up to date mostly been fragmented. The Lancet series recommended that all interested parties working to eliminate undernutrition should come together to review the structures that are currently in place; at how to simplify the current system; how to strengthen regional and sub-regional networks; and to develop a strategy to prioritise topics for research.[7] The path forward, from projects and evidence from randomised controlled trials to developing large scale programmes with sound design to achieve results, needs to be identified.[6]

Facility-based management of severe malnutrition

Probably the best known international initiative for the management of severe acute malnutrition is the WHO guideline, Ten Steps for the management of severe malnutrition; promoted as the standard by which severely malnourished children should be treated.[13,14]

The literature indicates that if implemented correctly, the protocol can improve case fatality rates from around 40% to the order of 1–5%.[4]

When reviewing the evidence on which the Ten Steps are based, it will be found that many studies were conducted in the 1960s and 1970s where it became clear that high protein and fluid intakes > 150 ml/kg during the initial phase increased mortality, and that careful feeding regimens initially increasing in volume and density toward a high energy formula to aid rapid catch up growth, reduced mortality.[15] These studies eventually led to the development of the WHO protocol.

In 2006 Brewster published a critical review of the evidence on which the WHO guideline is based. The review highlights a number of aspects where the WHO guidelines may be lacking in evidence and which may be important to consider. He pointed out that there is a lack of evidence that the high mortality rates are directly proportional to the quality of care and that the severity of illness is also largely a contributing factor. He also suggests that a protocol alone is not sufficient in adequately managing severe malnutrition, but that an experienced health worker made better clinical judgments than one who follows a protocol.[16] There appears to be support for recommendations made by the WHO on the necessity of routine

empirical antibiotic treatment, the prevention of hypoglycaemia through small frequent feeds, zinc supplementation, delayed iron supplementation, but that it may be preferable to provide smaller daily doses of vitamin A than a single large dose and that children with kwashiorkor may require more potassium than recommended.[16,15]

The F75 and F100 formulas as recommended by the WHO must also be evaluated critically. These formulae have a number of apparent shortcomings that need to be addressed. Both formulae have high osmolalities, namely 333 and 419 mOsml/l and lactose contents of 13 and 42 g/l respectively.[15] The importance of lactose intolerance in severely malnourished children tends to be downplayed. Enteropathy is often a feature of severe malnutrition and is usually accompanied with clinically significant carbohydrate intolerance with osmotic diarrhoea.[17]

It is uncertain what the rationale is for the very low protein content of the F75 formula at only 4,8% of energy as protein. An implication of the very low protein content is that the phosphorous requirements recommended by the WHO are not met.[15,17]

Another matter for concern in many countries with a high burden of severely malnourished children is the poor accessibility to the commercially F75 and F100 diets recommended by the WHO. So health facilities need to mix their own formulae and have to add their own mineral and vitamin mixes.[15] A matter that is not being considered, is the risk of nosocomial and food-related infections when milk formulae are prepared. In a study conducted in 2008 in 18 public health facilities in South Africa by the DOH, it was found that a vast majority of the samples of powdered infant formulae tested positive for pathogens after preparation, indicating inadequate hygiene during feed preparation.[18] It only stands to reason that a feed that requires a greater variety of constituents will run an even greater risk of being contaminated during preparation. Another shortcoming of mixing the formula from the recipe is that not all facilities have access to the vitamin and mineral mixes required to make up the micronutrient content. There is therefore a need for an affordable, hygienic and nutritional adequate alternative to the F75 and F100 recipes.

Brewster[17] pointed out that there are shortcomings in the guidelines in that the management of "marasmus" vs "kwashiorkor"; HIV negative and positive children; and teaching hospitals and rural hospitals are all "lumped" together. The WHO has confirmed that gaps in knowledge remain, particularly in the feeding of very young infants and also infants living with HIV/AIDS.[19]

Community-based therapeutic care

The area in the management of severe malnutrition that is enjoying considerable amount of attention is community-based therapeutic care.

Community-based care refers to treatment that is implemented at home with some external input such as a health worker.[20] Motivations for implementation of community-based therapeutic care include factors such as hospital budgetary constraints, bed shortages, the reduction of hospital-acquired infections and requests by families for early discharge due to concern for the care of other family members or loss of earnings.[20] One disadvantage to community-based care, is that the weight gain is often less than what is achieved during hospitalisation.

Community-based treatment occurs once the initial stabilisation phase during hospitalisation is completed. The initial stabilisation usually lasts two to seven days. Thereafter there are three main options for community-based care, namely: short-stay day care, rehabilitation at home with clinic visits, or rehabilitation at home with Ready to Use Therapeutic Foods (RUTF). There are advantages and disadvantages to all three option, and the option best suited to the situation should be considered.[20] The international trend seems to be toward the third option of rehabilitation at home with RUTF. The RUTF is a paste where part of the skim milk is replaced with a groundnut paste. It is more energy dense than the F100 formula, but has a similar nutrient to energy density ratio.[15,20] The advantages of the RUTF is that it does not support bacterial growth, can be consumed without the addition of water or processing, it is energy dense without the high osmolarity problem.[15] There is also some evidence that the RUTF supports better weight gain than the F100.[15,20] Limitations however to the RUTF are the high cost of the product, sharing of the product with other family members, compensatory reductions of home food and poor compliance.[15]

Community-based care will however only be effective if the infrastructure and adequate resources (including nutrition educators) are in place to provide the support to the mothers and caregivers after discharge. The mother or caregiver requires training on the importance of adequate feeding and rehabilitation at home and the child's monitoring either through home visits or at the clinic.[20] Therefore, optimal community-based rehabilitation requires careful planning and cannot be implemented without considerable initial inputs and resources being in place.[20]

References:

1. Briend A, Prudhon C, Prinzo ZW, Daelmans B, Mason JB. Putting the management of severe malnutrition back on the international health agenda. Food and Nutrition Bulletin 2006;27(3)supplement:S3–S6.
2. Black RE, Allen LH, Bhutta ZA, et al. Maternal and Child Undernutrition 1. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371:243–260.
3. UNICEF. Tracking Progress on Child and Maternal Nutrition [Online] 2009 [Access 2009, December 22]; Available: http://www.unicef.org/publications/index.html.
4. Collins S, Sadler K, Dent N, et al. Key issues in the success of community-based management of severe malnutrition. Food and Nutrition Bulletin 2006;27(3)supplement:S49–70.
5. Victora CG, Adair L, Fall C, et al. Maternal and Child Undernutrition 2: Maternal and Child Undernutrition: consequences for adult health and human capital. Lancet 2008;371:340–357.
6. Schultink W, Arabi M Effective Nutrition programming for children and the role of UNICEF: Conensus point from an expert Consultation. Food Nutr Bull 2009;30(2):189–196.
7. Morris SS; Cogill B; Uauy R. Maternal and Child Undernutrition 5: Effective international action against undernutrition: why has it proven so difficult and what can be done to accelerate progress? Lancet 2008;371:608–621.
8. Kleinert S & Horton R. South Africa's Health: departing for a better future? Lancet 25 August 2009 (published online) .
9. Draft Report: The nutritional status of children in the Western Cape (October 2009). University of Western Cape & Western Cape Department of Health (Unpublished data).
10. Bhutta Z, Ahmed T, Black RE, et al. Maternal and Child Undernutrition 3: What works? Interventions for maternal and child undernutrition and survival. Lancet 2009;371:417–440.
11. Bryce J, Coitinho D, Darnton-Hill I, Pelletier D, Pinstrup-Anderson P. Maternal and Child Undernutrition 4: Maternal and child undernutrition: effective action at national level. Lancet 2008; 371:510–526.
12. Chopra M, Lawn JE, Sanders D, et al. Achieving the Health Millennium Development Goals for South Africa: challenges and priorities. Lancet 25 August 2009 (published online).
13. WHO. Management of severe malnutrition: a manual for physicians and other senior health worker. [Online] 1999 [Access 2009, December 15]; Available: http://www.who.int/nutrition/publications/malnutrition/en/.
14. WHO. Guidelines for the inpatient treatment of severely malnourished children. [Online] 2003 [Access 2009, December 15]; Available: http://www.who.int/nutrition/publications/severemalnutrition/9241546093/en/index.html.
15. Brewster D. Critical appraisal of the management of severe malnutrition:2. Dietary management. Jnl Paed Child Health 2006;42:575–582.
16. Brewster D. Critical appraisal of the management of severe malnutrition: 1. Epidemiology and treatment guidelines. Jnl Paed Child Health 2006;42:568–574.
17. Brewster D. Critical appraisal of the management of severe malnutrition:3 Complications. Jnl Paed Child Health 2006;42:583–593.
18. Guidelines On Safe Preparation, Storage And Handling Of Powdered Infant Formula in Health Facilities And Home Environment. Draft 4 Department of Health 2009.
19. WHO Severe malnutrition: Report of a consultation to review current literature. [Online] 2004 [Access 2009, December 15]; Available: http://www.who.int/nutrition/publications/severemalnutrition/9241593318/en/index.html.
20. Ashworth A. Efficacy and effectiveness of community-based treatment of severe malnutrition. Food and Nutrition Bulletin 2006;27(3)supplement:S24–48.

The do's and don'ts of arginine supplementation

Chetty S
Department of Anaesthesiology, University of the Witwatersrand, Johannesburg, South Africa
Correspondence to: Dr Sean Chetty, e-mail: seanchetty@gmail.com

Abstract

In the last three decades the nutritional and pharmacologic effects of arginine have been the subject of intense investigation. Taking into consideration the many benefits that have been demonstrated from arginine supplementation, the question remains: "Can we afford not to supplement with this immuno-nutrient". The potential life-saving cardiovascular effects of arginine in both acute and chronic arginine supplementation has the ability to revolutionise the management of vascular disease, yet much more research must be done in this area. In addition, the proposed benefits of such supplementation in the sepsis model, makes arginine a very attractive model for decreasing the mortality statistics of this worldwide disease process. However, owing to the fact that arginine is a precursor for nitric oxide synthesis, the effects of which are potentially detrimental in the septic patient, further research is warranted in this field to determine the suitability of this agent in patient management.

S Afr J Clin Nutr 2010;23(1) Supplement:S25-S28

Introduction

Nutritional therapy (in critical care) has generally been designed to meet the body's nutritional needs for energy, protein and micronutrients. More recently, specialised nutritional supplements have been added to the standard enteral feeds to modulate the immune system. These nutrient supplements have been combined to form speciality enteral products referred to as immune-enhancing diets (IED). The body of literature supporting the use of IED has grown substantially in recent years and in 2001 consensus guidelines were developed by a panel of leading experts in the field.

There are a large number of these immuno-nutrients, each, or collectively, providing their own range of benefits for the critically ill patient. These include, but are not limited to, arginine, glutamine, omega fatty acids and selenium. Each of these compounds can be administered individually or combined with other nutritional support products.

Pharmaconutrition is a term that was coined by Heyland and colleagues[1] proposing that the administration of immuno-nutrients be dissociated from the provision of enteral nutrition so that their full dose can be delivered and their therapeutic effects evaluated appropriately without being influenced by the disruption of feeding regimens. This concept is important when one considers that the combination of immuno-nutrients and feeds results in sub-therapeutic doses of the former being administered due to interruptions of feeding. These interruptions are usually due to digestive intolerance, mechanical complications with feeding tubes, airway management, diagnostic procedures or infusion pump inaccuracies.

Arginine

Arginine is a non-essential amino-acid that is thought to become conditionally essential during growth and recovery following injury. It acts as a precursor of nitric oxide, polyamines (important in lymphocyte maturation) and nucleotides.

In the last three decades the nutritional and pharmacologic effects of arginine have been the subject of numerous studies.[2] Following initial work demonstrating that large doses of supplemental arginine possess immune-enhancing, wound-healing, and anti-tumour properties, there has been increased effort in defining possible clinical uses for arginine.[3]

Furthermore, the demonstration that arginine is the unique substrate for nitric oxide synthesis stimulated further research in this area, with particular focus on traumatic/haemorrhagic shock and sepsis.[4] However, nitric oxide has been implicated as one of the aetiological factors responsible for systemic vasodilation during the systemic inflammatory response syndrome (SIRS) and therefore the use of arginine in this situation could potentially worsen patient outcome.

Arginine metabolism

Arginine is a dibasic amino acid. It is considered to be a dietary conditionally dispensable amino acid. The average daily dietary consumption of arginine is 5–6 g. Under normal conditions, endogenous daily production of 15–20 g occurs via the citrulline intestinal-renal axis.[2]

A large proportion of arginine is used in protein synthesis, approximately 5% in urea synthesis, and a small portion (< 5%) is utilised by the nitric oxide synthase (NOS) enzyme system for

conversion to nitric oxide (NO). The intestinal absorption of arginine occurs via a transport system shared with lysine, ornithine, and cysteine. Arginine, ornithine, and lysine also share a common uptake and transport system in the brain, leukocytes, erythrocytes, fibroblasts, and leukocytes.[2]

The quantities of arginine produced normally are sufficient to maintain muscle and connective tissue mass. However, endogenous synthesis of arginine is insufficient to meet the heightened demands that increased protein turnover requires during periods of stress, such as critical illness. In such situations, arginine becomes indispensable for optimal growth and maintenance of positive nitrogen balance.[2]

Arginine also plays a key role within the urea cycle, the major pathway for ammonia detoxification. Arginase, the enzyme responsible for the catabolism of arginine in the urea cycle, has two distinct isoenzymes encoded by separate genes. **Type I arginase**, a cytosolic enzyme, is highly expressed in the liver as a component of the urea cycle, and is also present in wound-derived fibroblasts. **Type II arginase** is a mitochondrial enzyme expressed at lower levels in the kidneys, brain, small intestine, mammary glands, and macrophages. Any condition that increases demand for ammonia detoxification is likely to increase arginine requirements (Figure 1).[2]

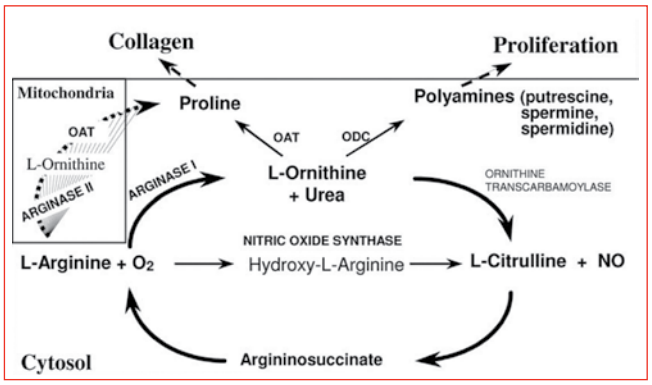


Figure 1: Metabolic pathways of arginine (OAT: ODC: NO:). *OAT,* ornithine aminotransgerase; *ODC,* ornithine decarboxylase; *No,* nitric oxide

This important pathway has been shown to be present in many tissues and cells including endothelium, brain, inflammatory cells (lymphocytes, macrophages, neutrophils, and mast cells), platelets, and hepatocytes. In addition to its role in vasodilatation, NO is a reputed neurotransmitter and cytotoxic effector molecule. NO is formed by oxidation of one of the two identical terminal guanidine groups of L-arginine, by NOS, a dioxygenase for which there are at least two identified isoforms. Both isoforms of NOS have been identified as flavoproteins, each containing flavine adenine dinucleotide and flavine adenine mononucleotide, and both are inhibited by diphenyleneiodonium, a flavoprotein inhibitor. Neuronal and endothelial NOS are expressed constitutively and are activated by Ca^{2+} /calmodulin. Inducible NOS is calcium independent and is expressed in response to inflammatory cytokines and endotoxins including interleukin-1, tumor necrosis factor-α, γ-interferon, and lipopolysaccharide.[2]

A third degradative pathway for arginine only recently has been described in mammalian tissues. This involves the decarboxylation of arginine to agmatine. The importance of this pathway in mammalian brain and other tissues is just beginning to be elucidated.[5]

Clinical Pharmacology of Arginine Supplementation

L-arginine is the precursor for the endogenous synthesis of NO due to the activity of NOS, which releases L-citrulline as a byproduct.[6,7,8] Although only a minor portion of L-arginine is metabolised via this pathway in vivo, it has attracted much interest in recent years because of the prominent role that NO plays in vascular physiology and pathophysiology. NO generated from L-arginine is a highly reactive radical gas and an important messenger molecule. At low concentrations like those produced by constitutive endothelial NOS (ecNOS) in the vasculature in vivo, NO acts as a paracrine-signaling molecule, mediating vasodilation,[9] inhibition of platelet activation,[10] inhibition of monocyte and leukocyte adhesion,[11] and inhibition of smooth muscle cell proliferation[12] and controlling vascular oxidative stress and the expression of redox-regulated genes.[13]

In certain animal models and in some human diseases, the biological functions of endothelium-derived NO are impaired, leading to dysregulation of endothelial control of vascular tone and blood flow. Such models include hypercholesterolaemic rabbits, rat models of hypertension, and hyperlipidaemic monkeys.[14] The mechanisms of this phenomenon are probably multi-factorial, including reduced NO elaboration by NOS, increased oxidative inactivation of NO, and enhanced formation of vasoconstrictor mediators like endothelin-1 and thromboxane A2.[14]

What then is the role of L-arginine in this setting?

NOS is inhibited by L-arginine analogs that are substituted at the guanidino nitrogen atom, like *N*G-monomethyl- L-arginine or *N*G-nitro-L-arginine.[15] Inhibitory action of these molecules is overcome by excess L-arginine,[15] indicating that there is competition for enzyme binding between L-arginine and its inhibitory analogs. Reduced activity of endothelial cell NOS was also shown to occur in the presence of low-density lipoprotein cholesterol; again, this effect can be overcome by excess L-arginine.[16] Although the mechanism of this latter phenomenon has not yet been fully elucidated, these data demonstrate that, under certain conditions, L-arginine availability regulates endothelial cell NOS activity.

Soon after these first animal experiments had demonstrated a beneficial effect of L-arginine on endothelial function, it was shown that local intracoronary infusion of L-arginine normalised coronary vasomotor responses to acetylcholine in hypercholesterolaemic humans.[17] A similar observation was also made upon systemic (intravenous) infusion of L-arginine in hypercholesterolaemic subjects, in whom endothelium-dependent forearm vasodilation was improved.[18] These are important findings, because endothelial dysfunction precedes angiographically visible atherosclerotic lesions in large coronary arteries.[19] Evidence from prospective clinical trials suggests that endothelial dysfunction is a predictor of future coronary events and therefore, reversal of endothelial dysfunction by L-arginine in vivo may suggest that this amino acid exerts anti-atherosclerotic effects in humans.[14]

Table I: Diseases in which L-arginine has been demonstrated to improve clinical end points of cardiovascular disease

Disease	L-arginine dose [a]	Effect
Peripheral Arterial Disease	3 x 8g/d iv 30g iv	Increased Walking distance[20] Increased Nutritive Muscle Blood Flow[21]
Coronary Artery Disease	3 x 3 g/d iv 3 x 2 g/d iv	Decreased Angina Symptom Score[22] Increased Exercise Capacity[23]
Congestive Heart Failure	5.6–12.6 g/d po	Increased Exercise Capacity[24]
Raynaud Syndrome	8.5 mg/min ia	Decreased Vasospasm Attacks[25]

'a – Routes of administration – iv = intravenously, po = orally, ia = intra-arterially

In addition to coronary artery disease, a number of studies have shown that oral L-arginine supplementation improves symptoms of certain vascular diseases as well (Table I).[14]

Although there is a bulk of evidence that supplementation with L-arginine—via the intra-arterial, intravenous, or oral route—improves endothelial dysfunction in hypercholesterolaemia and atherosclerosis, endothelial dysfunction in other cardiovascular diseases (like hypertension) was not shown to be consistently improved by L-arginine administration. Therefore, while there is great promise for this immune-nutrient is the treatment of vascular diseases, it is certainly not the panacea that the world seeks.

Arginine in sepsis

Sepsis is a major complication of an acute infection, triggered by a systemic inflammatory reaction. It is characterised by a reduction in plasma and tissue arginine levels compared with healthy individuals or nonseptic critically ill patients.[26,27,28] In addition, plasma amino acid levels are in general lower during sepsis, which is partly related to starvation due to limited nutritional protein supply, as well as to increased amino acid clearance[27] through gluconeogenesis, oxidation for energy supply, and protein synthesis in especially the liver and immune cells. This negative amino acid balance appears not to be compensated for by the excessive protein catabolism (protein breakdown is increased by 50% in septic patients) that occurs.

Recent evidence suggests that arginine metabolism in sepsis is disturbed in various aspects, probably related to the severity of the inflammatory response and induced by inflammatory mediators. In sepsis, the endogenous synthesis of arginine from the amino acid citrulline, is reduced to one third of the normal level.[28]

The rationale for arginine deficiency in sepsis is mainly based on the reduced arginine levels in sepsis that reflect the specific changes in arginine metabolism, with functional consequences regarding endothelial dysfunction, severe catabolism, impaired wound healing, and worse outcome. However, the direct effects of cytokines and hormones must also be considered in these pathophysiological processes as other amino acids can also be present in inadequate amounts.[29]

Only a few studies have investigated the effects of arginine supplementation in patients with sepsis. This exogenous arginine supplementation in sepsis shows controversial results with only limited data in humans and varying results in animal models of sepsis.

Since the severity of sepsis varies, and the route, timing, and dose of arginine differ between studies, it is difficult to draw a definitive conclusion for the effect of exogenous arginine supplementation in sepsis, based on these studies.

Although studies on arginine supplementation in septic patients are scarce, major risks of exogenous arginine are ascribed to the suggested increase in NO synthesis. Stimulated NO production is related to reduced blood pressure and is suggested to impair cardiac contractility, induce liver damage, and increase vascular permeability and bacterial translocation from the intestine. In addition, oxidative stress (through production of peroxynitrite- a harmful metabolite formed from NO and superoxide that nitrates the tyrosine residues in proteins to nitrotyrosine) and mitochondrial dysfunction are considered further risk factors of increased NO and, therefore, indirect results of exogenous arginine supply.

While enhanced NO production in sepsis is suggested to be related to the detrimental effects of hemodynamic instability and enhanced oxidative stress, potential mechanisms for beneficial effects of exogenous arginine supplementation in sepsis must also be considered. These include enhanced (protein) metabolism, improved (micro) circulation and organ function, effects on immune function and antibacterial effects, improved gut function, and an antioxidant role of arginine.

Taking these potential benefits into consideration and the fact that *Luiking et al*[30] have demonstrated that arginine can be given to septic patients without major effects on haemodynamics, more studies need to be done to determine the effects of arginine supplementation on septic patients.

Should we be supplementing arginine?

The benefits and side-effects of arginine supplementation tend to be related to the extent to which it influences the production of NO via the NOS pathway. As with any medication, over administration leads to undesirable effects which potentially lead to problems in the patient. This effect is made more obvious in patients where physiological homeostatic mechanisms are already at breaking point (such as in sepsis) (Figure 2).[31]

Taking into consideration the many benefits that have been demonstrated from arginine supplementation, the question remains: "Can we afford not to supplement with this immuno-nutrient".

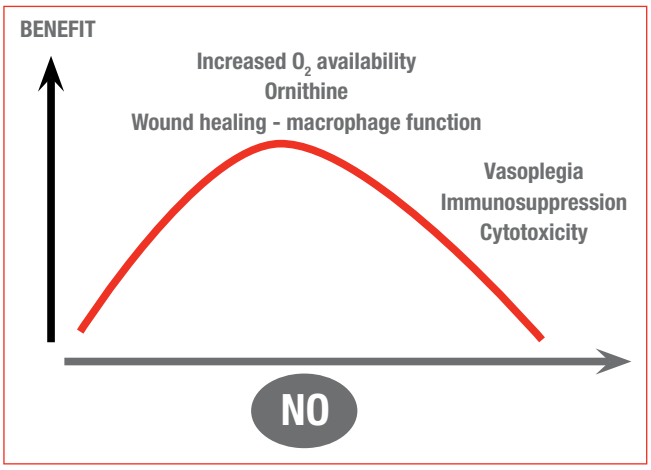


Figure 2: The beneficial and harmful effects of arginine supplementation. (*NO:* nitric oxide)

The potential life-saving cardiovascular effects of arginine in both acute and chronic arginine supplementation has the ability to revolutionise the management of vascular disease, yet much more research must be done in this area.

In addition, the proposed benefits of such supplementation in the sepsis model, makes arginine a very attractive model for decreasing the mortality statistics of this worldwide disease process. However, owing to the fact that arginine is a precursor for NO synthesis, the effects of which are potentially detrimental in the septic patient, further research is warranted in this field to determine the suitability of this agent in patient management.

Therefore, while both in-vitro and in-vivo work points towards arginine being a very useful immuno-nutrient in the management of both vascular diseases and sepsis, a lot more research must be done to determine not only the extent of the benefits of this therapy, but also the doses required to achieve these benefits. In addition safety data is lacking, especially with regards to the role of NO in the septic patient. The question remains: Will arginine supplementation lead to worsening of the inflammatory response in the septic patient?

In summary

The Do's – Keep abreast of the new research being done in the field of arginine supplementation and the potential benefits this therapy may provide.

The Don'ts – Be cautious and do not start your patient on supplemental arginine just yet. While there are potentially great therapeutic benefits in this treatment modality, its safety (especially in sepsis) is still to be consistently documented.

References

1. Pharmaconutrition: a new emerging paradigm. Jones NE, Heyland DK. 2008, Current Opin Gastroenterol, Vol. 24, pp. 215–222.
2. Use of Exogenous Arginine in Multiple Organ Dysfunction Syndrome and Sepsis. Barbul A, Uliyargoli A. 9 (Suppl), s.l. : Lippincott Williams & Wilkins, 2007, Critical Care Medicine, Vol. 35, pp. S564 – S567.
3. Arginine: Biochemistry, Physiology and Therapeutic Implications. Barbul A. 1986, Journal of Parenteral and Enteral Nutrition, Vol. 10, pp. 227–238.
4. Arginine Metabolism: Nitric Oxide and Beyond. Wu G, Morris SM Jr. 1998, Biochem J, Vol. 336, pp. 1–17.
5. Agmatine: At the Crossroads of Arginine Pathways. Satriano J. 2003, Ann NY Acad Sci , Vol. 1009, pp. 34–43.
6. Macrophage Syntehsis of Nitrite, Nitrate and N-nitrosamines: precursors and role of the respiratory burst. Iyengar R, Stuehr DJ, MArletta MA. 1987, Proc. Natl Acad. Sci, Vol. 84, pp. 6369–6373.
7. Vascular endothelial cells synthesis of nitric oxide from L-argenine. Palmer RMJ , Ashton DS, Moncada S. Nature, Vol. 333, pp. 664–666.
8. Arginine is a precursor of Endothelial derived Nitric Oxide. Schmidt HHHW, Nau H, Wittfoht W, Gerlach J, Prescher KE et al. European Journal of Pharmacology, Vol. 154, pp. 213 – 216.
9. Nitric Oxide accounts for the biological activity of endothelium derived relaxing factor. Palmer RMJ, Ferrige AG, Moncada S. Nature, Vol. 327, pp. 524–526.
10. An L-arginine/nitric oxide pathway present in human platelets regulates aggregation. Radomski MW, Palmer RMJ, Moncada S. Proc. Natl. Acad. Sci, Vol. 87, pp. 5193–5197.
11. Nitric Oxide: an endogenous modulator of leukocyte adhesion. Kubes P, Suzuki M, Granger DN. Proc. Natl. Acad. Sci., Vol. 88, pp. 4651–4655.
12. Nitric Oxide generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth mucscle cells. Garg UC, Hassid A. 1989, J Clin. Invest., Vol. 83, pp. 1774–1777.
13. Nitric oxide modulates the expression of monocyte chemoattractant protein-1 in cultured human endothelial cells. Zeiher AM, Fissthaler B, Schray-Utz B, Busse R. Circ Res, Vol. 76, pp. 980–86.
14. The Clinical Pharmacology of L-Arginine. Boger RH, Bode-Boger SM. 2001, Annual Review of Pharmacology and Toxicology, Vol. 1, pp. 79–99.
15. Characterisation of three inhibitors of endothelial nitric oxide synthase in vitri and in vivo. Rees DD, Palmer RMJ, Schulz R, Hodson HF, Moncada S. 1990, British Journal of Pharmacology, Vol. 101, pp. 746–752.
16. Native low density lipoprotein increases endothelial cell nitric oxide synthase generation of superoxide anion. Pritchard KA, Groszek L, Smalley DM, Sessa WC, Wu M et al. Circ. Res., Vol. 77, pp. 510–518.
17. Correction of Endothelial Dysfunction in coronary microcirculation of hypercholesterolaemic patients by L-arginine. Drexler H, Zeiher AM, Meinzer K, Just H. 1991, Lancet, Vol. 338, pp. 1546–1550.
18. L-arginine improves endothelium-dependant vasodilation in hypercholesterolemic humans. Creager MA, Gallagher SJ, Girerd XJ, Coleman SM, Dzau VJ, Cooke JP. 1992, J. Clin. Invest., Vol. 90, pp. 1248–1253.
19. Modulation of Coronary vasomotor tone in humans: progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Zeiher AM, Drexler H, Wollschlager H, Just H. 1991, Circulation, Vol. 83, pp. 391–401.
20. Restoring vascular NO formation by L-arginine improves the sypmtoms of intermittent claudication in patients with peripheral arterial occlusive disease. Boger RH, Bode-Boger SM, Thiele W, Creutzig A, Alexander K, Frohlich JC. Journal of American College of Cardiology, Vol. 32, pp. 1336–1344.
21. Dose related effect of intravenous L-arginine on muscular blood flowof the calf in patients with peripheral vascular disease. Schellong SM, Boger RH, Burchert W, Bode-Boger SM, Galland A et al. 1997, Clin. Sci, Vol. 93, pp. 159–165.
22. Long term L-arginine supplementation improves small vessel coronary artery endothelial funtion in humans. Lerman A, Burnett JC, Higano ST, McKinely LJ, Holmes DR. Circulation, Vol. 97, pp. 2123–2128.
23. Effect of Supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. Ceremuzynski L, Chamiec T, Herbaczynska-Cedro K. 1997, American Journal of Cardiology, Vol. 80, pp. 331–333.
24. Randomised, double-blind, placebo-controlled study of supplemental oral L-arginine in patients with heart failure. Rector TS, Bank AL, Mullen KA, Tschumperlin LK, Sih R et al. 1996, Circulation, Vol. 93, pp. 2135–2141.
25. Acute effect of nitric oxide on Raynaud's phenomenon in scleroderma. Freedman GR, Girgis R, Mayes MD. 1999, Lancet, Vol. 354, p. 739.
26. Plasma amino acids as predictors of the severity and outcome of sepsis. Freund H, Atamian S, Holroyde J et al. 1979, Ann. Surg., Vol. 190, pp. 571–576.
27. Amino Acid Kinetics in patients with sepsis. Druml W, Heinzel G, Kleinberger G. 2001, Americal Journal of Clinical Nutrition, Vol. 73, pp. 908–913.
28. Low Plasma Agrinine concentration in Septic Patients is related to diminished de novo arginine production from Citrulline. Luiking YC, Steens L, Poeze M et al. Supplement, 2003, Clinical Nutrition, Vol. 22, p. S26.
29. Plasma Arginine Correlations in trauma and Sepsis. Chiarla C, Giovannini I, Siegel JH. 2006, Amino Acids, Vol. 30, pp. 81–86.
30. L–agrinine infusion does not deteriorate the haemodynamic condition in patients with severe sepsis. Luiking YC, Poeze M, Hendrikx M et al. 2005, Clin Nutr., Vol. 24, pp. 612–613.
31. Metabolic Support in Sepsis and Multiple Organ Failure: More Questions than Answers. Vincent JL. 9 (Suppl), 2007, Critical Care Medicine, Vol. 35, pp. S436–S440.

New developments in clinical practice guidelines

Kreymann G
Baxter Healthcare, Deerfield, IL, USA
Correspondence to: Dr Georg Kreymann, e-mail: georg_kreymann@baxter.com

Abstract

During the last four years revised clinical practice guidelines on nutritional support have been published by the major nutritional societies worldwide. The aim of these guidelines is to promote the safe and effective care of patients who need nutritional support as part of their overall management. All guidelines are based on the available "best evidence" in order to assist nutrition professionals in making decisions on the appropriate and cost-effective nutritional practices. Although such guidelines are a useful tool to patient management, they are meant to support, not replace, the clinical judgment and experience of nutrition professionals.

S Afr J Clin Nutr 2010;23(1) Supplement:S29-S32

During the last four years revised clinical practice guidelines have been published by the major nutritional societies: The American Society of Enteral and Parenteral Nutrition (ASPEN),[1] the European Society for Clinical Nutrition and Metabolism (ESPEN)[2–11] and the Canadian Critical Care Clinical Practice Guidelines Committee (CCPG)[12] with latest updates from www.criticalcarenutrition.com.

These guidelines agree on most points concerning the nutritional support of critical ill patients and will be outlined in a short form. Any discrepancies will be highlighted. This outline follows the structure of the most recent ASPEN guideline.[1] Due considerations relating to special diagnoses have not been incorporated in this paper.

Enteral nutrition

Which patient

All: Enteral nutrition (EN) is the preferred form of nutrition support in the critical ill patient who is unable to maintain volitional intake.

ESPEN: It should be given to all patients who are not expected to be on a full oral diet within 3 days.

Timing of enteral nutrition

All: EN should be started within the first 24–48 hours following admission.

Route of enteral feeding

All: Either gastric or small bowel feeding is acceptable in the ICU setting. Critically ill patients should be fed via an enteral access tube placed in the small bowel if at high risk for aspiration or after showing intolerance to gastric feeding (high gastric residual volumes). According to ESPEN, jejunal feeding is likely to be the best option when it can be easily implemented (post abdominal trauma or elective abdominal surgery).

CCPG: The routine use of small bowel feedings is recommended in units where obtaining small bowel access is feasible.

Dosage of enteral feeding

ASPEN: The feedings should be advanced toward the patient's goal over the next 48–72 hours. Energy requirements may be calculated by predictive equations or measured by indirect calorimetry. Efforts to provide > 50%–65% of goal energy should be made in order to achieve the clinical benefit of EN over the first week of hospitalisation.

ESPEN: No general amount can be recommended as EN therapy has to be adjusted according to the progression/course of the disease and to gut tolerance. During the acute and initial phase of critical illness an exogenous energy supply in excess of 20–25 kcal/kg BW/day may be associated with a less favourable outcome. During recovery (anabolic flow phase), the aim should be to provide 25–30 total kcal/kg BW/day.

- **Controversy:**

  ASPEN/CCPG: If unable to meet energy requirements (100% of target goal energy) after 7–10 days by the enteral route alone, consider initiating supplemental parenteral nutrition (PN). Initiating supplemental PN prior to this 7–10 day period in the patient already receiving EN does not improve outcome and may be detrimental to the patient.

  ESPEN: All patients who do not meet their nutritional needs after 2 days should receive supplemental PN.

Protein requirements

ASPEN: In patients with body mass index (BMI) < 30, protein requirements should be in the range of 1.2–2.0 g/kg actual body weight per day, and may likely be even higher in thermally injured or multi-trauma patients.

Obese patients

ASPEN: In the critically ill obese patient, permissive underfeeding or hypocaloric feeding with EN is recommended. For all classes of obesity where BMI is > 30, the goal of the EN regimen should not exceed 60%–70% of target energy requirements or 11–14 kcal/kg actual body weight per day (or 22–25 kcal/kg ideal body weight per day). Protein should be provided in a range ≥ 2.0 g/kg ideal body weight per day for Class I and II obese patients (BMI 30–40), and ≥ 2.5 g/kg ideal body weight per day for Class III obese patients (BMI ≥ 40).

Haemodynamically unstable patients

ASPEN: In the setting of haemodynamic compromise (patients requiring significant haemodynamic support including high dose catecholamine agents, alone or in combination with large volume fluid or blood product resuscitation to maintain cellular perfusion), EN should be withheld until the patient is fully resuscitated and/or stable.

Monitoring tolerance and adequacy

ASPEN: In the ICU setting, evidence of bowel motility (resolution of clinical ileus) is not required in order to initiate EN in the ICU. In the ICU patient population, neither the presence nor absence of bowel sounds nor evidence of passage of flatus and stool is required for the initiation of enteral feeding.

Patients should be monitored for tolerance of EN (determined by patient complaints of pain and/or distention, physical exam, passage of flatus and stool, abdominal radiographs). Inappropriate cessation of EN should be avoided. Holding EN for gastric residual volumes < 500 mL in the absence of other signs of intolerance should be avoided.

ESPEN/CCPG: IV administration of metoclopramide or erythromycin should be considered in patients with intolerance to enteral feeding e.g. with high gastric residuals.

ASPEN/CCPG: Use of enteral feeding protocols increase the likelihood of overall attainment of percentage of goal energy provided and should be implemented.

ASPEN: Patients placed on EN should be assessed for risk of aspiration. Steps to reduce risk of aspiration should be employed.

In all intubated ICU patients receiving EN, the head of the bed should be elevated 30°–45°. Use of chlorhexidine mouthwash twice a day should be considered to reduce risk of ventilator-associated pneumonia. Blue food colouring and glucose oxidase strips, as surrogate markers for aspiration, should not be used in the critical care setting.

ASPEN: Development of diarrhoea associated with enteral tube feedings warrants further evaluation for aetiology. If there is evidence of diarrhoea, soluble fibre containing or small peptide formulations may be utilised.

Immune-modulating enteral formulations

ASPEN/ESPEN: Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, ω-3 fatty acids, and antioxidants) should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis. ICU patients not meeting criteria for immune-modulating formulations should receive standard enteral formulations.

To receive optimal therapeutic benefit from the immune-modulating formulations, at least 50%–65% of goal energy requirements should be delivered daily.

CCPG: Based on 4 level 1 (A) studies and 17 level 2 (B) studies, we recommend that diets supplemented with arginine and other select nutrients not be used for critically ill patients.

ALL: Patients with ARDS and severe acute lung injury (ALI) should be placed on an enteral formulation characterised by an anti-inflammatory lipid profile (i.e. ω-3 fish oils, borage oil) and antioxidants.

Probiotics

- **Controversy:**
  ASPEN: Administration of probiotic agents has been shown to improve outcome (most consistently by decreasing infection) in specific critically ill patient populations involving transplantation, major abdominal surgery, and severe trauma. No recommendation can currently be made for use of probiotics in the general ICU population due to a lack of consistent outcome effect. It appears that each probiotic species may have different effects and variable impact on patient outcome, making it difficult to make broad categorical recommendations. Similarly, no recommendation can currently be made for use of probiotics in patients with severe acute necrotising pancreatitis, based on the disparity of evidence in the literature and the heterogeneity of the bacterial strains utilised.
  CCPG: There are insufficient data to make a recommendation on the use of prebiotics/probiotics/synbiotics in critically ill patients.

Antioxidant vitamins and selenium

ASPEN/CCPG: A combination of antioxidant vitamins and trace minerals (specifically including selenium) should be provided to all critically ill patients receiving specialised nutrition therapy.

There are insufficient data to make a recommendation regarding IV/PN selenium supplementation alone, or in combination with other antioxidants, in critically ill patients.

Glutamine (enteral)

All: The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) should be considered in thermally injured, trauma, and mixed ICU patients.

Soluble fibre

ASPEN: Soluble fibre may be beneficial for the fully resuscitated, haemodynamically stable critically ill patient receiving EN who develops diarrhoea. Insoluble fibre should be avoided in all critically ill patients. Both soluble and insoluble fibre should be avoided in patients at high risk for bowel ischaemia or severe dysmotility.

CCPG: There are insufficient data to support the routine use of fibre (pectin or soy polysaccharides) in enteral feeding formulae in critically ill patients.

Parenteral nutrition

General indication

ASPEN: A critically ill ICU patient may be an appropriate candidate for PN under certain circumstances: (i) The patient is well nourished prior to admission, but if after 7 days of hospitalisation EN has not been feasible or target energy goal has not been met consistently by EN alone, (ii) On admission, the patient is malnourished and EN is not feasible, (iii) A major surgical procedure is planned, the preoperative assessment indicates that EN is not feasible through the perioperative period, and the patient is malnourished.

ESPEN: All patients who are not expected to be on normal nutrition within 3 days should receive PN within 24– 48 h, if EN is contraindicated or if patients cannot tolerate EN.

Patients without malnutrition

- **Controversy:**
  ASPEN: If early EN is not feasible or available the first 7 days following admission to the ICU, no nutrition support therapy (i.e. standard therapy) should be provided. In the patient who was previously healthy prior to critical illness with no evidence of protein-energy malnutrition, use of PN should be reserved and initiated only after the first 7 days of hospitalisation (when EN is not available).
  ESPEN: In patients who tolerate EN and can be fed approximately to the target energy values no additional PN should be given. In patients who cannot be fed sufficient enterally the deficit should be supplemented parenterally. In patients intolerant to EN, PN may be proposed at a level equal to but not exceeding the nutritional needs of the patient. Overfeeding should be avoided.

Patients with malnutrition

ASPEN: If there is evidence of protein-energy malnutrition on admission and EN is not feasible, it is appropriate to initiate PN as soon as possible following admission and adequate resuscitation.

ESPEN: Patients with a severe undernutrition should receive EN up 25–30 total kcal/kg BW/day. If these target energy values are not reached, supplementary PN should be given.

Central or peripheral access

ESPEN: A central venous access device is often required to administer the high osmolarity PN mixture designed to cover the nutritional needs fully. Peripheral venous access devices may be considered for low osmolarity (< 850 mOsmol/L) mixtures designed to cover a proportion of the nutritional needs and to mitigate negative energy balance.

All-in-on bags

ESPEN: PN admixtures should be administered as a complete all-in-one bag.

Dosing

ASPEN: In all ICU patients receiving PN, mild permissive underfeeding should be considered at least initially. Once energy requirements are determined, 80% of these requirements should serve as the ultimate energy goal or dose of parenteral feeding. Eventually, as the patient stabilises, PN may be increased to meet energy requirements. For obese patients (BMI ≥ 30), the dose of PN with regard to protein and energy provision should follow the same recommendations given for EN.

ESPEN: During acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease negative energy balance. In the absence of indirect calorimetry, ICU patients should receive 25 kcal/kg/day increasing to the energy target over the next 2–3 days.

CCPG: In critically ill patients who are not malnourished, are tolerating some EN, or when PN is indicated for short term use (< 10 days), low dose PN should be considered. There are insufficient data to make recommendations about the use of low dose PN in the following patients: those requiring PN for long term (> 10 days), obese critically ill patients, and malnourished critically ill patients. Practitioners will have to weigh the safety and benefits of low dose PN on an individual case-by-case basis in these latter patient populations.

Parenteral nutrition supplementary to enteral nutrition

- **Controversy:**

  ASPEN: A critically ill ICU patient may be an appropriate candidate for PN under certain circumstances:

  (i) The patient is well nourished prior to admission, but after 7 days of hospitalisation, EN has not been feasible or target energy goal has not been met consistently by EN alone.

  ESPEN: All patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary PN.

  CCPG: We recommend that PN not be started at the same time as enteral nutrition. In the patient who is not tolerating adequate enteral nutrition, there are insufficient data to put forward a recommendation about when PN should be initiated.

Carbohydrates

ESPEN: The minimal amount of carbohydrate required is about 2 g/kg of glucose per day.

Glucose control

ASPEN: A protocol should be in place to promote moderately strict control of serum glucose when providing nutrition support therapy. A range of 6– 8 mg/dL may be most appropriate.

ESPEN: Hyperglycaemia (glucose > 10 mmol/L) contributes to death in the critically ill patient and should also be avoided to prevent infectious complications. Reductions and increases in mortality rates have been reported in ICU patients when blood glucose is maintained between 4.5 and 6.1 mmol/L. No unequivocal recommendation has been reported in ICU patients when blood glucose is maintained. There is a higher incidence of severe hypoglycaemia in patients treated to the tighter limits.

Canadian Guidelines: We recommend that hyperglycaemia (blood sugars > 10 mmol/L) be avoided in all critically ill patients. Based on the NICE-SUGAR study and a recent meta-analysis, we recommend a blood glucose target of around 8.0 mmol/L (or 7–9 mmol/L), rather than a more stringent target range (4.4 to 6.1 mmol/L) or a more liberal target range (10 to 11.1 mmol/L).

Lipids

ASPEN/Canada: In the first week of hospitalisation in the ICU, when PN is required and EN is not feasible, patients should be given a PN formulation without soy-based lipids.

ESPEN: Lipid emulsions should be an integral part of PN for energy and to ensure essential fatty acid provision in long-term ICU patients. The tolerance of mixed LCT/MCT lipid emulsions in standard use is sufficiently documented. Several studies have shown specific clinical advantages over soybean LCT alone but require confirmation by prospective controlled studies. Olive oil-based PN is well tolerated in critically ill patients. Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes. Fish oil-enriched lipid emulsions probably decrease length of stay in critically ill patients. Intravenous lipid emulsions (LCT, MCT or mixed emulsions) can be administered safely at a rate of 0.7 g/kg up to 1.5 g/kg over 12–24 h.

Amino acids

ESPEN: When PN is indicated, a balanced amino acid mixture should be infused at approximately 1.3–1.5 g/kg ideal body weight per day in conjunction with an adequate energy supply.

Canadian Guidelines: In critically ill patients who are receiving PN, there are insufficient data to make a recommendation regarding the use of branched chain amino acids.

Glutamine (parenteral)

All: When PN is indicated in ICU patients the amino acid solution should contain 0.2–0.4 g/kg/day of L-glutamine (e.g. 0.3–0.6 g/kg/day alanyl-glutamine dipeptide).

Micronutrients

All: All PN prescriptions should include a daily dose of multivitamins and of trace elements.

Efforts to initiate enteral feeding

ASPEN: In patients stabilised on PN, periodically repeated efforts should be made to initiate EN. As tolerance improves and the volume of EN energy delivered increases, the amount of PN energy supplied should be reduced. PN should not be terminated until ≥ 60% of target energy requirements are being delivered by the enteral route.

References

1. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr 2009;33(3):277–316.
2. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 2006;25(2):210–223.
3. Singer P, Berger MM, Van den Berghe G, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr 2009;28:387–400.
4. Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006;25(2):224–244.
5. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr 2009;28:378–386.
6. Anker SD, John M, Pedersen PU, et al. ESPEN Guidelines on Enteral Nutrition: Cardiology and pulmonology. Clin Nutr 2006;25(2):311–318.
7. Anker SD, Laviano A, Filippatos G, et al. ESPEN Guidelines on Parenteral Nutrition: on cardiology and pneumology. Clin Nutr 2009;28:455–460.
8. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN Guidelines on Enteral Nutrition: Adult renal failure. Clin Nutr 2006;25(2):295–310.
9. Cano NJ, Aparicio M, Brunori G, et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. Clin Nutr 2009;28:401–414.
10. Meier R, Ockenga J, Pertkiewicz M, et al. ESPEN Guidelines on Enteral Nutrition: Pancreas. Clin Nutr 2006;25(2):275–284.
11. Gianotti L, Meier R, Lobo DN, et al. ESPEN Guidelines on Parenteral Nutrition: pancreas. Clin Nutr 2009;28:428–435.
12. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 2003;27(5):355–373.

Nutrition in paediatric Crohn's disease

Goulet O, MD, PhD
Department of Pediatric Gastroenterology, Hepatology and Nutrition, National Reference Center for Rare Digestive Diseases
Intestinal Failure Rehabilitation Center, Hôpital Necker – Enfants Malades, Paris, France, niversity of Paris-Descartes
Correspondence to: Prof Olivier Goulet, e-mail: olivier.goulet@nck.ap-hop-paris.fr
Keywords: Crohn's disease; linear growth; Tumour Necrosis Factor-α; nutritional support; enteral feeding; immunomodulation, Growth failure, target size, puberty, enteral feeding, immunosuppressive therapy, anti-TNF

Abstract

Inflammatory bowel disease (IBD) such as Crohn's disease (CD) results from the interaction between an individual's immune response and precipitant environmental factors, which generate an anomalous chronic inflammatory response in those who are genetically predisposed. Protein-energy malnutrition (PEM) is a frequent consequence of CD. Macrophage products such as Tumour Necrosis Factor-α (TNF-α) and interleukins 1 and 6 may be the central molecules that link the inflammatory process to derangements of homeostasis. CD is associated with frequent nutritional deficiencies, the pattern and severity of which depends on the extent, duration and activity of the inflammation. Nutritional support is especially important in childhood CD as an alternative to pharmacological treatment, especially steroids. Current treatment regimens limit the use of corticosteroids, by using immunomodulatory drugs, recommend the use of enteral nutrition, and, if necessary, consider surgery for intestinal complications of localised CD. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among children whose growth remained compromised with previously available therapies. For all treatment modalities, there is a window of opportunity to achieve normal growth before puberty is too advanced.

S Afr J Clin Nutr 2010;23(1) Supplement:S33-S36

Crohn's disease CD manifests during childhood or adolescence. Protein-energy malnutrition (PEM) is a frequent consequence of CD.[1–3] PEM in childhood and adolescence leads to failure to thrive and deficit in final height. According to different studies and to diagnosis delays, linear growth is reduced in one to two third of affected children at the time of diagnosis. However, comparison between populations is difficult because the definition of growth retardation varies according to different studies.[1–3] Protracted PEM with subsequent failure to thrive is associated with an impairment in the achievement of the final target size. In addition, protracted use of steroids and/or insufficient control of the disease activity may further impair growth and body composition.

Primary therapy for CD, has two aims, namely i) the control of the inflammatory process, as assessed by the the paediatric Crohn's disease activity index (PCDAI) as well as ii) the correction or the prevention of malnutrition and failure to thrive. One of the "peculiarities" of CD is the ability of nutritional therapy to achieve both of them. Growth is fundamental to the practice of paediatrics, so by taking growth as the primary outcome measure in this chronic inflammatory disease, an important issue is addressed for the patients and their families as well as for paediatricians.

Factors inducing malnutrition and failure to thrive

Several associated factors are responsible for PEM, including poor oral intake, intestinal malabsorption, increased gut losses from protein losing enteropathy, increased nutrient requirements, increased protein turn over, and drug nutrient interactions (Table I).[4–11] Energy and protein substrates are diverted into the inflammatory process, thus weight loss, and linear growth as well as pubertal development in children are notably retarded. There is considerable controversy about nutritional needs during phases of active and inactive disease. It is, for example, often assumed that in acute illness a child requires increased nutritional support, however the precise relationship between illness severity and energy expenditure is uncertain. Measurement of resting energy expenditure (REE) and

Table I: Causes of malnutrition in Crohn's disease

Reduced oral intake
Disease induced anorexia
Restrictive diet/iatrogenic
Intestinal malabsorption
Decreased absorptive surface (mucosal injury)
Bile salt deficiency (ileal disease)
Intraluminal bacterial overgrowth
Increased intestinal losses
Protein-losing enteropathy
Blood loss
Electrolytes, minerals, trace elements (fistula)
Increased requirements
Increased energy expenditure (sepsis, fever, tissue repair)
Impaired protein metabolism (inflammation, cytokines)
Drug-nutrient interactions
Corticosteroids (calcium, protein)
Cholestyramine (fat, fat soluble vitamins)
Sulphasalasine

its relationship with disease activity in children with inflammatory bowel disease has provided conflicting results.[6–9]

Macrophage products such as Tumour Necrosis Factor-α (TNF-α) and interleukins 1 and 6 may be the central molecules that link the inflammatory process to derangements of homeostasis.[12,13] An association between impaired growth in children with CD and low IGF-I levels is well recognised. Early studies emphasised the role of malnutrition in the suppression of IGF-I production. Insulin-like growth factor I (IGF-I), produced by the liver in response to growth hormone (GH) stimulation, is the key mediator of GH effects at the growth plate of bones.[14] However, a simple nutritional hypothesis fails to explain all the observations related to growth in children with CD. The direct, growth-inhibitory effects of pro-inflammatory cytokines are increasingly being recognised and explored. In rats with trinitrobenzenesulphonic acid-induced colitis, 40% of growth impairment was attributable to inflammation, with the rest being due to undernutrition.[15] In transgenic mice without inflammation, raised IL-6 retards growth and suppressing insulin-like growth factor (IGF)-I.[16]

Steroid dependency and their side effects when used for a long period, justify the need to limit their use. The permanent height deficit documented in children with CD seems to be directly linked to the duration of steroid treatment and to the age of diagnosis or the localisation of the disease.[17,18] Whatever the consequences on the final height, which vary from one study to another, the consideration of the quality of the bone mineralisation has now become of a greater concern in relation to both the degree and the persistence of inflammation as well as the long-term use of steroids.[19]

Enteral feeding

CD is associated with frequent nutritional deficiencies, the pattern and severity of which depends on the extent, duration and activity of the inflammation. Nutritional support allows these deficiencies in energy, macro- and micro-nutrients to be corrected. Enteral feeding (EF) is a primary therapy for CD, as it allows the inflammatory activity to be controlled and the patient to be kept in remission. Nutritional support is especially important in childhood CD as an alternative to pharmacological treatment, especially steroids. O'Morain et al were the first to perform a controlled study in acute CD showing that EF based on an elemental diet was as effective as steroids, with remission rates of 81 and 80%, respectively.[20] Subsequent prospective controlled trials have confirmed the therapeutic efficacy of EF, even if the published meta-analyses of EF as primary therapy in CD reported only a modest advantage for steroids.[21–24] However, the value of nutritional support in the correction and maintenance of nutritional status is widely accepted.[25]

Enteral feeding (EF) has been traditionally proposed in the proximal localisation of the disease where its efficacy has been documented. However, many cases with disease involving the colon have been reported.[26,27] The therapeutic effect of EF is multifactorial (Table II). Whether or not the type of enteral feeds is elemental, oligopeptides (protein hydrolysate) or whole protein may influence the result of EF still remains the subject of debate.[28,29] Intriguingly, there is also increasing evidence that an aggressive nutritional programme may in itself be sufficient to reduce the mucosal inflammatory response. EF alone may reduce many pro-inflammatory cytokines to normal, and allow mucosal healing.[30,31] In addition, specific nutritional components, such as n-3 polyunsaturated fatty acids, may have an anti-inflammatory effect as they may alter the pattern of leukotrienes generated during the immune response.[32] Several other factors have also been thought to determine the response to EF (Table II). Recent studies have emphasised the role of anti-inflammatory cytokine such as transforming growth factor-beta (TGFb) present in the diet. A polymeric diet (Modulen IBD®, Nestlé®) rich in tTGFb2 is now widely used as a single nutrient and has been shown to induce remission in children with active CD.[33] We have recently reported the beneficial effects of this diet in children regardless of the route of administration orally or by gastric tube feeding.[34] Moreover, Lionetti et al studied intestinal microbiota in children receiving full EF using Modulen IBD® for 8 weeks.[35] In 8 out of 9 children, the exclusive EF alone induced disease remission. In 1 child, steroids were added to achieve remission. In all children, analysis of gel band distribution revealed profound modification of the intestinal microbiota after exclusive EF. These data suggest that a possible mechanism of action of EF in inducing disease remission in CD is the capacity of modification of intestinal microbiota. Possible explanations of such capacity are both low residue and prebiotic properties of the polymeric liquid formula. In another study, exclusive EF was shown to reduce bacterial diversity and to initiate a sustained modulation of all predominant intestinal bacterial groups.[36] Exclusive EF may reduce inflammation through modulating intestinal Bacteroides species. The implications of these results for exclusive EF therapy and CD pathogenesis has became an important area of research.

Table II: Mode of action of enteral feeding in Crohn's disease

- Bowel rest
- Reduced intestinal secretions
- Low antigenic load
- Decreased intestinal permeability
- Anti-inflammatory effect of diet (transforming growth factor-beta (TGFb2)
- Modification of intestinal microbiota
- Trophic nutrients
- Improved nutritional status

Phenotype as well as genotype of the disease have been thought to influence the response to EF. Buchanan et al reported an 8-week course of primary exclusive EF in 114 children, median age at diagnosis was 11.6 years.[37] Disease phenotype was assigned using published classifications. Inflammatory markers and anthropometry (Z-scores) were calculated before and after treatment. Fifty-seven children (51.8%) were fed orally whilst 53 (48.2%) were fed by tube. Eighty-eight children (80%) achieved remission. Patients in remission had comparative improvements in weight and BMI Z-scores by the end of treatment. Individuals with isolated terminal ileal disease ($N = 4$) had lower remission rates than children in whom CD affected other locations ($P = 0.02$). No other significant differences in remission rates for any other disease locations were found. The authors concluded that EF nutrition induced clinical remission, normalisation of inflammatory markers and improved weight/BMI Z-scores in most patients. This study demonstrated that disease phenotype should not influence clinicians when commencing patients on exclusive EF.[37]

It has also been recently reported that the response to treatment with systemic steroids, AZA/6-MP and infliximab are not related to NOD2/CARD15 mutations, age of diagnosis and disease behaviour. Patients with colonic disease seem to have higher rates of steroid dependency.[38]

Although the totality of the evidence is not consistent, available data suggest that EF may be useful for maintaining remission in patients with CD. Large randomised controlled trials are necessary to assess definitively the efficacy of EF in the maintenance of CD remission.[39]

Parenteral nutrition

In the early 1970s, it was postulated that "bowel rest" achieved by the administration of parenteral nutrition (PN) might be of primary importance in the treatment of CD. Many trials since then examined this theory, but the results were difficult to interpret because of major methodological flaws. Greenberg et al achieved a prospective, controlled trial to compare directly the efficacy of TPN with continuous EF as a primary therapy in patients with CD[40] and found similar short term remission rates and long-term outcomes in patients receiving either treatment.[41–43]

The role of intraluminal nutrients and the preservation of the intestinal mucosal barrier function seems very important and makes the use of TPN questionable. Thus, TPN can no longer be regarded as having a role in the primary treatment of active uncomplicated CD. Its use in complicated disease remains, but probably in an adjunctive rather than a therapeutic role (Table III).

Table III: Indications for parenteral nutrition

- Severe fulminant enterocolitis
- Enteral feeding or steroid resistance
- Complication
  - *intestinal stenosis*
  - *fistula*
- Severe anoperineal disease
- Perioperative management

Immunosuppressive therapies influencing growth

Early forms of CD in children are usually severe because of the diagnostic challenges, the extent of the lesions and CD's duration. In the adolescent or the young adult it is now possible to predict the outcome of the disease based on the extent and severity of the lesions at the time of the first CD episode. [44] CD can be considered to be a lifetime disease with a major risk of extension and growth impairment. Childhood CD therefore requires a therapeutic approach, even more so when discovered early, which aims to limit long-term use of steroids and surgery. In a long term therapeutic strategy CD cases in very young children might justify the wider and earlier use of immunosuppressive drugs such as azathioprine, 6-mercaptopurine or methotrexate in view of the documented efficacy of these drugs in maintaining remission in serious and/or steroid dependent CD cases in adults as well as in children.[45–48]

The efficacy of infliximab as maintenance therapy in patients with otherwise chronically active CD is well established. Data concerning linear catch up growth following anti-TNF therapy are now available. In a cohort of 32 children and adolescents (63% males; mean age 13.4 years, range 4.7–17.3) with chronically active CD, despite immunomodulatory and prior corticosteroid therapy, were commenced on infliximab therapy. [49] Growth parameters standardised for age, gender, and pubertal development prior to and following infliximab therapy were compared. In all, 28 of 32 patients tolerated and responded to the induction regimen and 27 responders continued to receive infliximab via regularly scheduled infusions (n = 22) or episodically (n = 5) for a median of 26 months. Mean standard deviation score (SDS) for height at the time of initiation of infliximab therapy was -1.15 +/- 1.2 and had declined despite the use of other therapies from -0.44 +/- 1.1 at initial diagnosis. Increases in height velocity and stature during infliximab therapy were limited by pubertal stage: Tanner I-III: DeltaSDS for height velocity was +3.94, for height +/-0.50, ($P < 0.001$); Tanner IV, V: DeltaSDS for height velocity +0.22, for height +/- 0.02, (P = NS). The authors concluded that height velocity improved and height centile increased during infliximab therapy provided patients were treated prior to or in early puberty. These data support the use of infliximab in young patients with otherwise refractory disease, and suggest that ultimate height in this subset of children with severe CD may be less compromised than with previous therapies.[49] A recent prospective study involved 176 children (mean age 10.1 years; 65% male) younger than 16 years old at diagnosis and Tanner I to III during the study. They had mild (33%) or moderate/severe (67%) disease at diagnosis. [50] Clinical and growth data were prospectively obtained during the study. First-year treatments included immunomodulators (60%), corticosteroids (77%), 5-aminosalicylates (61%), anti-TNF (15%), and EF (10%).Disease activity at one year was inactive/mild (89%) or moderate/severe (11%). By two years, 86% had received immunomodulators and 36% anti-TNF. Mean height Z-scores at diagnosis, one year, and two years were -0.49 +/- 1.2 standard deviations (SDs), -0.50 +/- 1.2, and -0.46 +/- 1.1, respectively. Of the subjects, 10%, 8%, and 6.5% had height Z-scores less than -2 SD at diagnosis and 1 year, and 2 years of treatment respsectively. A height velocity Z-score less than -1SD was seen in 45% of subjects at one year and 38% at two years. The mean height velocity Z-score, however, increased between one and two years from -0.71 to 0.26 ($P < 0.03$). Duration of corticosteroid use longer than six months in the first year of treatment was associated with abnormal height velocity at one year. Interestingly, no statistically significant effect on height velocity Z-scores was noted when comparing those receiving or not receiving infliximab. The persistent growth delay despite improved disease activity and the frequent use of immunomodulators and biologics suggests that additional strategies are needed to improve growth outcomes. Although surgery has been shown to improve growth velocity, it does not prevent relapse.[51] Thus surgery should be used only in refractory and limited CD resistant to anti-TNF treatment.

Introduction of rhGH therapy in children was associated with a cessation in the deterioration in linear growth. However, an improvement in height SDS was not observed over the period of the study.[52] Future studies should explore the efficacy of a higher dose of rhGH in CD. Because of the unfavourable cost and side effects of rhGH considerations, it is now probably preferable to avoid long term steroid treatment and/or to use nutritional therapy whose efficacy has been documented in children.[53]

Conclusions

The severity and course of the cases diagnosed before the age of 10 must be taken into account in the therapeutic strategy. Current treatment regimens limit the use of corticosteroids, by using immunomodulatory drugs, recommend the use of enteral nutrition, and, if necessary, and consider surgery for intestinal complications of localised CD. Biologic agents with the potential for mucosal healing hold promise of growth enhancement even among children whose growth remained compromised with previously available therapies. Treatments, such as anti-TNF, are now becoming more widely used and may offer advantages in promoting growth. There remains, however, a need for large, multi centre studies of the different treatment options in paediatric CD. One should emphasise the importance of using standardised measurements of growth, such as height velocity standard deviation scores and height standard deviation scores as outcome measures to monitor progress in response to treatment. For all treatment modalities, there is a window of opportunity to achieve normal growth before puberty is too advanced.

References

1. Walters TD, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. Nat Rev Gastroenterol Hepatol. 2009;6:513–23.
2. Sentongo TA, Semeao EJ, Piccoli DA, Stallings V A, Zemel BS. Growth, body composition and nutritional status in children and" adolescents with Crohn's disease. J Pediatr Gastroenterol Nutr 2000;31:33–40.
3. Savage MO, Eeattie RM, Caillacho-Hubner C, Walker-Sillith JA, Sanderson IR. Growth in Crohn's disease. Acta Paediatr Suppl 1999;88:89–92.
4. Motil KJ, Grand RJ, Maletskos CJ, Young VR. The effect of disease, drug and diet on whole body protein metabolism in adolescents with Crohn disease and growth failure. J Pediatr 1982;101:345–51,
5. Thomas AG, Miller V, Taylor F, et al. Whole body protein turnover in childhood Crohn's disease. Out 1992;33:675–7.
6. Zoli G, Katelaris PH, Garrow J, et al. Increased energy expenditure in growing adolescents with Crohn 's disease. Dig Dis Sci 1996;41:1754–9.
7. Varille V, Cézard JP, de Lagausie P, et al. Resting energy expenditure before and after surgical resection of gut lesions in pediatric Crohn ' s disease. J Pediatr Gastroenterol Nutr 1996;23:13–9.
8. Mingrone G, Capristo E, Greco A V, et al. Elevated diet-induced therrnogenesis and lipid oxidation in Crohn disease. Am J Clin Nutr 1999;69:325–30.
9. Wiskin AE, Wootton SA, Culliford DJ, Afzal NA, Jackson AA, Beattie RM. Impact of disease activity on resting energy expenditure in children with inflammatory bowel disease. Clin Nutr. 2009 Jun 8. [Epub ahead of print]
10. Nishi Y, Lifshitz F, Eayne MA, et al. Zinc status and its relation to growth retardation in children with inflamrnatory bowel disease. Am J Clin Nutr 1980;33:2613–21.
11. Rannem T, Ladefoged K, Hylander E, et al. Selenium status in patients with Crohn's disease, Am J Clin Nutr 1992;56:933–7.
12. Levine A, Shamir R, Wine E, Weiss B, Karban A, Shaoul RR, et al. TNF promoter polymorphisms and modulation of growth retardation and disease severity in pediatric Crohn's disease. Am J Gastroenterol. 2005;100:1598–604.
13. Wong SC, Macrae VE, McGrogan P, Ahmed SF. The role of pro-inflammatory cytokines in inflammatory bowel disease growth retardation. J Pediatr Gastroenterol Nutr. 2006;43:144–55.
14. Ballinger AB, Azooz O, El-Haj T, Poole S, Farthing MJ. Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of undernutrition in a rat model of colitis. Gut. 2000;46:694–700.
15. Sawczenko A, Azooz O, Paraszczuk J, Idestrom M, Croft NM, Savage MO, Ballinger AB, Sanderson IR. Intestinal inflammation-induced growth retardation acts through IL-6 in rats and depends on the -174 IL-6 G/C polymorphism in children. Proc Natl Acad Sci U S A. 2005;102:13260–5.
16. De Benedetti F, Meazza C, Oliveri M, Pignatti P, Vivarelli M, Alonzi T, Fattori E, Garrone S, Barreca A, Martini A. Effect of IL-6 on IGF binding protein-3: a study in IL-6 transgenic mice and in patients with systemic juvenile idiopathic arthritis. Endocrinology. 2001;142:4818–26.
17. Newby EA, Sawczenko A, Thomas AG, Wilson D. Interventions for growth failure in childhood Crohn's disease. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003873.
18. Navarro FA, Hanauer SB, Kirschner BS. Effect of long-term low-dose prednisone on height velocity and disease activity in pediatric and adolescent patients with Crohn disease. J Pediatr Gastroenterol Nutr. 2007;45:312–8.
19. Semeao EI, Jawad AF, Stouffer NO, Zemel BS, Piccoli DA, Stallings VA. Risk factors for low bone mineral density in children and young adults with Crohn's disease. J Pediatr 1999;135:593–600.
20. O'Morain C, Segal A W, Levi AJ, Valman HB. Elemental diet in acute Crohn's disease. Arch Di.s. Child 1983;53:44– 7.
21. Griffiths AM, Oh1sson A, Sherrnan PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment ofactive Crohn's disease. Gastroenterology 1995;108:1056–67.
22. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of active Crohn's disease. Gastroenterology 1995;108:1056–67.
23. Griffiths AM. Enteral nutrition: the neglected primary therapy of active Crohn's disease. J Pediatr Gastroenterol Nutr 2000;31:3–5.
24. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. Cochrane Database Syst Rev. 2001;(3):CD000542.
25. Escher JC, Taminiau JA, Nieuwenhuis EE, Büller HA, Grand RJ. Treatment of inflammatory bowel disease in childhood: best available evidence. Inflamm Bowel Dis. 2003;9:34–58.
26. Ruemmele FM, Roy CC, Levy E, Seidman EG. Nutrition as primary therapy in pediatric Crohn's disease: fact or fantasy ? J Pediatr 2000; 136:285–91.
27. Heuschkel RB, Walker-Smith JA. Enteral nutrition in inflammatory bowel disease of childhood. JPEN 1999;23: S29–S32.
28. Teahon K, Smethurst P, Pearson M, et al. The effect of elemental diet on intestinal permeability and inflammation in Crohn's disease. Gastroenterology 1991;101:84–9.
29. Beattie RM, Schiffin EJS, Donnet-Hughes A, et al. Polymeric nutrition as the primary therapy in children with small bowel Crohn 's disease. Aliment Pharmacol Therap 1994;8:609–15.
30. Breese EJ, Michie CA, Nicholls SW, et al. The effect of treatment of lymphokine-secreting cells in the intestinal mucosa of children with Crohn's disease. Aliment Pharmacol Therap 1995;9:547–53.
31. Fell JM, Paintin M, Donnet-Hughes A, Arnaud-Battandier F, MacDonald TT, Walker-Smith JA. Remission induced by a new specific oral polymeric diet in children with Crohn's disease. Nestle Nutr Workshop Ser Clin Perform Programme. 1999;2:187–96.
32. Belluzi A, Brignola C, Campieri M, et al. Effect of an enteric coated fish-oil preparation on relapses in Crohn's disease. N EnglJ Med 1996;334:1557–60.
33. Hartman C, Berkowitz D, Weiss B, Shaoul R, Levine A, Adiv OE, et al. Nutritional supplementation with polymeric diet enriched with transforming growth factor-beta 2 for children with Crohn's disease. Isr Med Assoc J. 2008;10:503–7.
34. Rubio A, Talbotec C, Garnier H, Schmitz J, Syhan J, Goulet O, Ruemmele F. Efficacy of fractioned oral vezrsus continuous enteral nutritional therapy in pediatric Crohn's disease. J Pediatr Gastroenterol Nutr 2009; (Abstract)
35. Lionetti P, Callegari ML, Ferrari S, Cavicchi MC, Pozzi E, de Martino M, Morelli L. Enteral nutrition and microflora in pediatric Crohn's disease. JPEN J Parenter Enteral Nutr. 2005;29(4 Suppl):S173–5.
36. Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS. Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease. Aliment Pharmacol Ther. 2008 Sep 15;28(6):724–33.
37. Buchanan E, Gaunt WW, Cardigan T, Garrick V, McGrogan P, Russell RK. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. Aliment Pharmacol Ther. 2009 1;30:501–7.
38. Weiss B, Lebowitz O, Fidder HH, Maza I, Levine A, Shaoul R, Reif S, Bujanover Y, Karban A. Response to Medical Treatment in Patients with Crohn's Disease: The Role of NOD2/CARD15, Disease Phenotype, and Age of Diagnosis. Dig Dis Sci. 2009 Aug 20. [Epub ahead of print]
39. Yamamoto T, Nakahigashi M, Umegae S, Matsumoto K. Enteral nutrition for the maintenance of remission in Crohn's disease: a systematic review. Eur J Gastroenterol Hepatol. 2009 Aug 24. [Epub ahead of print]
40. Greenberg OR, Fleming CR, Jeejeebhoy KN, et al. Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. Gut 1988;29:1309–15.
41. Layden T, Rosenberg I, Nemchausky B, et al. Reversal of growth arrest in adolescents with Crohn's disease after parenteral alimentation. Gastroenterology 1976;70:1017 –21.
42. Strobel CT, Byme WI, Ament ME. Home parenteral nutrition in children with Crohn's disease: an effective management alternative. Gastroenteroiogy 1979;77: 272–9.
43. Lake AM, Kim S, Mathis RK, Walker W A. Influence of preoperative parenteral alimentation on post-operatirve growth in adolescent Crohn's disease. J Pediatr Gastroenterol Nutr 1985;4:182–6
44. Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135:1106–13.
45. Feagan BG, Fedorak RN, Irvine J, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. N Engl J Med 2000 ;342:1627–320.
46. Lloyd Still JD. Azathioprine and the treatment of chronic inflammatory bowel disease. J Pediatr 1990; 117: 732–5.
47. Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. J Pediatr 1990;117:809–14.
48. Markowitz J, Grancher K, Kohn N, Lesser M, Daum F and the pediatric 6MP collaborative group. A multicenter trial of 6-mercaptopurine and prednisone In children with newly diagnosed Crohn's disease. Gastroenterology 2000;119:895–902.
49. Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. Inflamm Bowel Dis. 2007 4:424–30.
50. Pfefferkorn M, Burke G, Griffiths A, Markowitz J, Rosh J, Mack D, et al. Growth abnormalities persist in newly diagnosed children with crohn disease despite current treatment paradigms. J Pediatr Gastroenterol Nutr. 2009;48:168–74.
51. McLain BI, Davidson PM, Stokes KB, Beasley SW. Growth after gut resection for Crohn's disease. Arch Dis Child 1991;65:370–6.
52. Wong SC, Hassan K, McGrogan P, Weaver LT, Ahmed SF.The effects of recombinant human growth hormone on linear growth in children with Crohn's disease and short stature. J Pediatr Endocrinol Metab. 2007;20:1315–24.
53. Heuschkel R. Enteral nutrition should be used to induce remission in childhood Crohn's disease. Dig Dis. 2009;27:297–305.

Nutritional implications of food allergies

Steinman H
FACTS: Food & Allergy Consulting & Testing Services
Correspondence to: Dr Harris Steinman, e-mail: harris@factssa.com

Abstract

Food allergy is becoming an increasing problem worldwide, with an estimated 6–8% of children affected at some point in their childhood. It is important to recognise that the nutritional implications encompass not only the elimination of essential food(s) from the diet (and the consequent attendant lack of energy, protein or other macro or micro constituents, including vitamins), but that undiagnosed or poorly managed conditions such as severe hayfever or asthma may result in decreased activity, and/or increased or decreased food intake, which in turn may cause either negative effects on growth, or obesity. Clinical awareness is required among health professionals as to the clinical characteristics, epidemiology, investigation, and management of food allergic disorders, as is the inclusion of a dietitian as part of the allergy team. Good dietary intervention in children (and adults) with single or multiple food allergies should be seen as an integral part of the allergy consultation. It remains an essential part of holistic care.

S Afr J Clin Nutr 2010;23(1) Supplement:S37-S41

Food allergy is becoming an increasing problem worldwide, with an estimated 6–8% of children affected at some point in their childhood. However, consumer surveys indicate that the perceived prevalence of food allergy is even higher; 20–30% of the people interviewed consider that they or a family member have an allergy to a food product, and around 22% implement some form of an elimination diet, which may or may not be required, on the mere possibility that the food may contain an allergen.[1,2] For example, milk elimination diets are frequently adopted in the treatment of atopic dermatitis when the actual prevalence of cow's milk allergy in patients on milk elimination diets may be significantly lower than the number of patients prescribed such diets.[2] Elimination of any major food, without considering its nutritional implications, has the potential to result in harm. In fact there are a number of scenarios which may impact adversely on the diet of an individual and/or other family members (Table I).

Table I: Scenarios of presumed food allergy with nutritional implications

- Poorly managed condition
- Undiagnosed condition
- No elimination diet implemented
- Excessively restrictive diet implemented
- Cross-reactive foods not eliminated
- Non-relevant but potential cross-reactive foods removed
- Hidden allergens involved
- Behaviour or psychological factors
- Tactile-defensive children
- Significant social chaos
- Nutrition misinformation
- Food faddism
- Cultural preferences
- Alternative nutrition therapies
- Alternative diagnostic allergy tests
- Misconceptions

It is important to recognise that the nutritional implications encompass not only the elimination of essential food(s) from the diet (and the consequent attendant lack of energy, protein or other macro or micro constituents, including vitamins), but that undiagnosed or poorly managed conditions such as severe hayfever or asthma may result in decreased activity, and/or increased or decreased food intake, which in turn may cause either negative effects on growth, or obesity. Alternative concepts of health, as published in the media, may result in diets self-selected by children with behavioural disorders, or parent-selected from nutrition misinformation, cultural preferences, alternative nutrition therapies, or misconceptions about food tolerance.[3] For example, the author was referred a 6-week-old infant fed rooibos tea alone, as a result of misinformation regarding the infant's first feeding.

Behavioural conditions may also play a role, with feeding refusal and protein-energy malnutrition secondary to food allergies having been described.[4] A South African study highlighted the higher incidence of allergies among tactile-defensive children compared to the norm. Tactile-defensive children eat only a limited range of foods.[5]

Importantly, lack or removal of a responsible food allergen may result in the exacerbation or manifestation of other atopic conditions, such as asthma, allergic rhinitis, atopic dermatitis, and other food allergies.[6]

Accurate diagnosis is essential to prevent the imposition of unnecessarily restrictive diets, particularly on young children, although our adult patients should also be considered. However, there are a number of difficulties in making the correct diagnosis, including that not all allergies to food are IgE-mediated, with approximately 30% being delayed non-IgE-mediated.[7,8] This is particularly problematic when children present with possible multiple food allergies, and is exacerbated where the presenting pathology is a mixture of IgE-mediated and non-IgE-mediated disease. Even with double-blind placebo-controlled challenges, isolated delayed responses may occur in over 12% of challenge tests.[9,10] A further difficulty is the poor understanding of test interpretation, with diets being implemented based on sensitisation to foods that may in fact not result in the elicitation of symptoms.[11,12]

It is also relevant to remember that food proteins may be encountered directly, through oral consumption, or indirectly, via either transmission in breast milk or through inhalational or epicutaneous skin contact.[13,14]

Poorly managed condition or undiagnosed condition

It is self-evident that an undiagnosed food allergy may result in poor absorption of energy, protein, or other essential nutrients. For example, chronic diarrhoea may result in villus-flattening, directly affecting the absorption of these vital substances. Not always appreciated is that poorly-managed conditions or other undiagnosed allergies may affect appetite, with consequent attendant adverse effects. For example, poorly-managed asthma, severe hay fever or eczema may result in tiredness, apathy, and decreased appetite, with consequent weight loss, failure to thrive, or height retardation. Alternately, though appetite is not affected, exercise may be decreased, which may result in a child who is overweight or obese.

Lactating women restricting allergens

Although the elimination of allergens from the diet of women with babies at high risk for allergies is no longer recommended, many lactating mothers choose to restrict the intake of various allergens during lactation. For example, mothers may restrict milk intake, to assist their breastfed milk-allergic infants. However, this may have unintended consequences that become clinically significant; particularly if a mother's mean levels of calcium and vitamin D intake are below the adequate intake level. Milk restriction has been shown to compromise protein and the intake of other nutrients in lactating women who restricted milk to < 250 ml per day, affecting vitamin D, calcium, thiamin, riboflavin and zinc intake.

Vitamin D levels in breast milk vary between 20 and 60 IU/l,[15] which is well below the recommended intake of 200 IU/l for all breastfed and bottlefed infants.[16] Higher quantities of vitamin D might be required by dark-skinned infants, or mothers wearing traditional modest dress, due to the poor formation of vitamin D by the skin.[16]

Some experts suggest that milk restriction should not be recommended during lactation; and where this is unavoidable, nutrients provided by milk should be compensated for by other foods or supplements, practice that should not be followed without expert advice.[17]

Restrictive food diets

The institution of un-monitored dietary restrictions, as a result of misdiagnosis or over-zealous management, may also impact on growth and nutrient intake.[18,19] Dietary limitations secondary to food allergy may lead to failure to thrive, and/or deficiencies in specific macro- and micronutrients.[20] Elimination diets in particular are potentially hazardous to children, with cases of rickets, kwashiorkor, and vitamin and mineral deficiency having been reported in the literature.[18,21,22,23,] Lack of parental education and basic health knowledge may influence the correct implementation of restrictive diets.

Cows' milk allergy is one of the most common allergies in infancy, real or assumed. Approximately 2–3% of young children develop allergy or intolerance to cow's milk. The only available treatment is elimination of milk from the diet, but a milk-free diet may not meet the child's nutritional needs adequately. Children on milk-free diets have been reported to have significantly lower intake of energy, fat, protein, calcium, riboflavin and niacin.[20] Use of milk substitutes improved the nutritional content of the cow's milk-free diets; however, the recommendations for riboflavin and calcium were still not met, and supplements with calcium, vitamin D and riboflavin were indicated.[20]

Other studies have reported retardation of height in cow's milk-allergic children, low serum zinc values, and low serum iron concentration. Dietary intake of energy may be below the recommendation in some children, even though protein intake is high. Some children had low intakes of riboflavin.[24] Children with cow's milk allergy who experienced relative length or height decrease after the onset of symptoms of food allergy experienced no catch-up growth by 24 months of age.[6,24,25]

Children with two or more food allergies have been shown to be shorter and to consume less calcium and vitamins, particularly vitamins D and E, than those with one food allergy or age-matched controls.[21,26] This effect was lessened if the child received dietetic support.[21]However, growth impairment is also reported in children with other allergic conditions, such as asthma and atopic dermatitis.[27,28,29] Standing height retardation and delayed skeletal maturity scores may be significant.[27]

Both vitamin D-deficient rickets and calcium-deficient rickets are well-described, separate entities, and have been reported in children with cows' milk allergy who are not receiving adequate supplementation.[6,30,31,32,33] Seizures secondary to hypocalcaemia have been reported.[7] There is a strong correlation between iron-deficient anaemia and vitamin D deficiency[34]; therefore, if one is present, the potential lack of the other should be investigated. It has also been shown that treatment with iron alone leads to rising levels of vitamin D, suggesting that iron deficiency might be a factor in vitamin D deficiency.[35,36]

Whole-body bone mineral content (BMC) and bone mineral density (BMD) have been shown to be reduced for age in children with cow's milk allergy by more than four years. Reduced bone mineralisation also occurred. Bone age was retarded by a mean 1.4 years.[37] Dietary calcium deficiency may increase fracture risk, though it is uncertain whether the association was due to the illness, calcium deficit or a deficit in other milk nutrients.[38]

Although uncommon, scurvy and pellagra have been documented as consequences of food allergy.[39] Scurvy (vitamin C deficiency) was reported in a 34-year-old man with a history of rhinitis and severe oral allergy syndrome for multiple fruits and vegetables. He had restricted his diet to milk, beef and oats. Scurvy developed nine years after onset of his allergy.[40] Although most individuals with oral allergy syndrome (OAS) are not allergic to all fruits and vegetables, it is important to assess whether these patients are at risk of any vitamin deficiencies.

Although rare, cases of kwashiorkor unrelated to chronic illness have been reported in affluent families. In 12 children with kwashiorkor evaluated in seven tertiary referral centres in the United States, most cases were due to nutritional ignorance, perceived milk intolerance, or food faddism. Half were the result of a deliberate deviation to a protein-deficient diet because of a perceived intolerance to formula or milk. Homes with significant social chaos were a factor in a few.[22] Kwashiorkor was described in a 22-month-old child who had been weaned onto a rice beverage at 13 months of age. The rice beverage, fallaciously referred to as rice milk, was extremely low in protein content. Kwashiorkor resulting from the use of a non-dairy creamer as a milk alternative has been described.[41]

Nutritional deficiency may also occur in adults, in particular with sensitisation to multiple foods and if a restrictive diet is self-imposed.[42] Importantly, specific food-restrictive diets may have specific attendant risks; for example, children with peanut or tree nut allergy may need to find other sources of potassium, children with wheat allergy need to ensure satisfactory iron intake, and soybean allergy requires consideration of zinc intake. Egg allergy may require attention to vitamin B12 intake.

Family and parental beliefs

Parental beliefs about food allergies may lead to dietary restrictions severe enough to cause failure to thrive in their children, in particular if the health care provider collaborates with these unsubstantiated parental beliefs.[43] Significantly, parental misconceptions and health beliefs concerning what constitutes a normal diet for infants may in themselves be a cause of failure to thrive. In one study, seven patients (aged 7 to 22 months) evaluated for poor weight gain and linear growth were found to be consuming only 60% to 94% of the recommended energy intake, because of parental restriction. Parents were concerned that their children would become obese, develop atherosclerosis, become junk food dependent, and/or develop unhealthy eating habits.[44]

Psychology

One cannot consider the nutritional implications of food allergies without considering the psychological effects of the disease on the child, siblings and parents, particularly in the setting of very restrictive diets, or if the individual is at risk of anaphylaxis. Not only will the psychological sequelae encompass the whole family, but the dietary requirements for the affected individual will affect the whole family: avoiding peanuts will require full family participation. Restrictive diets may also have an impact on the quality of life and anxiety of the allergic child, the parents and siblings.[45] In older children, risk-taking behaviour may occur; precautionary labelling of the presence of hidden allergens may be ignored, with the attendant effects on the parents.

Lactose/sucrose/fructose

As a result of an allergy diagnosis (particularly asthma), health care providers may restrict the intake of additives and preservatives, in particular when associated with soft drinks. A consequence of this has been the replacement of these drinks with fruit juice. However, excess fruit juice consumption may result in chronic diarrhoea and be a contributing factor in nonorganic failure to thrive. Iron deficiency may also be a consequence.[46]

Milk substitutes

A number of products are marketed as suitable replacements for cow's milk, including extensively-hydrolysed milk, soy milk, rice milk, and goat's milk. Occasionally parents may regard non-dairy creamers as suitable replacements. These are not without risks.

For example, vitamin D or calcium deficiency, resulting in rickets, may be caused by the replacement of milk with non-dairy creamer, or soy milks that are not adequately fortified. This is exemplified by a case report of a 17-month-old male, breastfed until 10 months of age, when he was weaned to a soy health food beverage. The soy beverage was not fortified with vitamin D or calcium. Intake of solid foods was good, but included no animal products. Although total daily energy intake was 114% of the recommended dietary allowance, dietary vitamin D intake was essentially absent because of the lack of vitamin D-fortified milk. He had limited sun exposure, and his dark complexion further reduced endogenous skin synthesis of vitamin D. At around 10 months, he had an almost complete growth arrest of both height and weight, and regression in gross motor milestones. Clinical features of rickets were present.[41]

Extensively-hydrolysed hypoallergenic formulae are designed to be tolerated by infants with cow's milk allergy, yet around 10% of infants will not tolerate these products; if health professionals continue not to take this important consideration into account , adverse nutritional effects are likely.[47] Furthermore, it is suggested that in children with IgE-mediated cow's milk allergy, the first ingestion of extensively-hydrolysed cow's milk protein formulas should require strict medical supervision, because of the potential of immediate reactions.[48]

Similarly, 20–40% of children with IgE-mediated cow's milk allergy, and up to 60% of infants with non-IgE-mediated cow's milk allergy, will not tolerate soya milk.[49]

Rice and oat milk have poor energy and protein content (rice milk 0.4 g/100 ml and oat milk 1.0 g/100 ml protein) compared to cow's milk-based infant formulae (1.9 g/100 ml).[50] However, rice and oat milk may be used as a suitable alternative to cow's milk in older children, with adequate growth, on diets which are otherwise nutritionally sound.

Companies have marketed goat's milk as a suitable alternative for cow's milk-allergic individuals, but as with other mammalian milks including mare, buffalo, and ewe, the majority of such milks cross-react with cow's milk protein and hence are not suitable for children with cow's milk protein allergy.[51,52,53,54] Up to 90% of children with cow's milk allergy will be cross-reactive to goat's milk.[55] Allergy may

occur to goat's milk and sheep's milk without concomitant allergy to cow's milk.[56] However, for the 10% of patients that tolerate goat's protein, goat's milk may be an excellent substitute in children older than two years.[57]

Undiagnosed conditions

Undiagnosed or inadequately-managed allergic conditions may have severe nutritional implications for the patient. Particularly hazardous are conditions such as eosinophilic oesophagitis, which has become increasingly prevalent over the past decade.[58] Unfortunately, gastrointestinal manifestations of food allergy are varied, with well-described clinical entities being recognised, many of which are not initially attributed to food.[59] Protein-losing enteropathy is a feature of both non-IgE-mediated allergic enteropathy disorders as well as of the eosinophilic gastroenteritis disorders (mixed IgE and non-IgE). In food protein-induced enteropathy, failure to thrive, iron deficiency anaemia and hypoproteinaemia is common.[59] In eosinophilic gastroenteritis, growth retardation, protein-losing enteropathy, and growth failure occurs. Serum-specific IgE is present in approximately 50%.[60]

Multiple food protein intolerance is a severe form of immune reaction. One of the cardinal features of this spectrum is a failure to tolerate extensively-hydrolysed formula or soya-based formula. Infants may react to a wide range of foods, including proteins within breast milk and other foods normally considered of 'low allergenic potential', such as rice.[61] An amino acid formula is the formula of choice in such cases, as up to 10% of these infants will react to the extensively-hydrolysed casein or whey formulae.[62,63,64,65]

Although eczema is a multifactorial disease, IgE and non-IgE food reactions may play an important role. Avoidance of specific foods is often based on belief, and proper diagnosis should be implemented.[66]

Coeliac disease, although not an allergy, is immune-mediated. It is a very under-diagnosed condition, as symptoms may be latent. In these individuals, failure to thrive is the major feature. All children with failure to thrive with no obvious cause should be evaluated for this condition.[67]

Although uncommon, biotin deficiency has been encountered in infants weaning from breast- and formula feeding.[68,69] Biotin deficiency has been described in an infant fed with amino acid formula and hypoallergenic rice. The amino acid formula was not supplemented with biotin, since biotin was not permitted as a food additive in that country.[70]

Alternative diagnostic allergy tests

A number of unproven or scam allergy tests are being marketed, including the ALCAT, IgG, Vega (BEST) testing, hair analysis, and many others which may lead to nutritional implications as a result of misdiagnosis.[71,72,73,74] Dietary recommendations implemented may result in responsible foods for allergic reactions not being removed from the diet; or more commonly, the implementation of unnecessarily restrictive diets. In a study, double-blind placebo-controlled, food challenge (DBPCFC) was only rarely in agreement with the alternative test, and many patients did not have any food allergy.[75] Alternative health practitioners may implement blanket recommendations that may be unnecessary, e.g. removing wheat, milk, sugar, and other foods without adequate confirmation of a cause and effect relationship, which may result in unintended nutritional deficiencies.

Conclusions

Good dietary intervention in children (and adults) with single or multiple food allergies should be seen as an integral part of the allergy consultation. It remains an essential part of holistic care.[7,76]

Children diagnosed with food allergies need an annual nutrition assessment to prevent growth disorders or inadequate nutrient intake. Children with milk allergies or multiple food allergies are at greater risk.[21] In the management of an infant with cow's milk allergy, ideally breastfeeding should continue (if tolerated) for as long as possible, under the supervision of a dietitian to ensure nutritional adequacy, with supplementation and weaning onto other solids from six months of age (World Health Organization recommendation).[77]

Both new and old patients need to be reviewed. A clear strategy regarding allergy re-assessment, testing, and challenge needs to be implemented, with close follow-up and dietary supervision. The dietary recommendations need to be tailored to the individual child, taking into account the overall nutritional requirements, the risk of reaction on re-exposure, and the natural history of the specific food allergy in question as regards the likelihood of persistence versus outgrowing. Timing of food challenge tests will depend on the clinical history, type of food allergen, and demonstration of declining specific IgE levels. Cross-reactivity with other foods needs to be carefully evaluated, and only cross-reactive foods clearly resulting in adverse clinical effects should be removed.

It is recommended that a few-foods diet is followed for no more than 10–14 days, as it is not nutritionally adequate. Elimination diets should be supervised and monitored to a degree similar to that for drug treatment, and the need for continued dietary elimination should be reviewed on a regular basis and food re-challenges should considered.[78] Health care providers must be vigilant in monitoring both growth and feeding patterns to identify inappropriate dietary changes that may result in nutritional deficiencies.

Clinical awareness is required among health professionals as to the clinical characteristics, epidemiology, investigation, and management of food allergic disorders, as is the inclusion of a dietitian as part of the allergy team.

References:

1 Sloan AE, Powers ME. A perspective on popular perceptions of adverse reactions to foods. J Allergy Clin Immunol 1986;78:127–33.

2 Sinagra JL, Bordignon V, Ferraro C, Cristaudo A, Di Rocco M, Amorosi B, Capitanio B. Unnecessary milk elimination diets in children with atopic dermatitis. Pediatr Dermatol 2007;24(1):1–6.

3 Kirby M, Danner E. Nutritional deficiencies in children on restricted diets. Pediatr Clin North Am 2009;56(5):1085–103.

4 Fortunato JE, Scheimann AO. Protein-energy malnutrition and feeding refusal secondary to food allergies. Clin Pediatr (Phila) 2008;47(5):496–9.

5 Smith AM, Venter DJL, Naidoo NT, Roux S. The incidence of confirmed allergies among a group of tactile-defensive children. Current Allergy Clin Immunol 2004;17(1):15–9.

6 Yu JW, Pekeles G, Legault L, McCusker CT. Milk allergy and vitamin D deficiency rickets: a common disorder associated with an uncommon disease. Ann Allergy Asthma Immunol 2006;96(4):615–9.

7 Noimark L, Cox HE. Nutritional problems related to food allergy in childhood. Pediatr Allergy Immunol 2008;19(2):188–95.

8 Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. J Pediatr Gastroenterol Nutr 2000;30:S87–94.

9 Breuer K, Heratlzadeh A, Wulf A, et al. Late eczematous reactions to food in children with atopic dermatitis. Clin Exp Allergy 2004;34(5):817–24.

10 Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2001;107:548–53.

11 Sampson HA. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. JACI 1997;100:444–51.

12 Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting open food challenges to milk, egg and peanut in children. Clin Exp Allergy 2000;30:1541–6.

13 Høst A, Husby S, Hansen LG, Osterballe O. Bovine beta-lactoglobulin in human milk from atopic and non-atopic mothers. Relationship to maternal intake of homogenized and unhomogenized milk. Clin Exp Allergy 1990;20(4):383–7.

14 Van Reijsen FC, Felius A, Wauters EA, Bruijnzeel-Koomen CA, Koppelman SJ. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. J Allergy Clin Immunol 1998;101(2):207–9.

15 Hollis BW, Roos BA, Draper HH, Lambert PW. Vitamin D and its metabolites in human and bovine milk. J Nutr 1981;111:1240–8.

16 Pettifor JM. Nutritional rickets: deficiency of vitamin D, calcium, or both? Am J Clin Nutr 2004;6 (Suppl.):1725S–9S.

17 Mannion CA, Gray-Donald K, Johnson-Down L, Koski KG. Lactating women restricting milk are low on select nutrients. J Am Coll Nutr. 2007;26(2):149–55.

18 Huang LT, Yang W, Wu CL. Vitamin D deficiency rickets due to inappropriate feeding: report of one case. Acta Paediatr Taiwan. 2000;41(3):151–4.

19 Warner JO. The UK allergy paradox. Pediatr Allergy Immunol 2004;15:287–8.

20 Henriksen C, Eggesbø M, Halvorsen R, Botten G. Nutrient intake among two-year-old children on cow's milk-restricted diets. Acta Paediatr. 2000;89(3):272–8.

21 Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth.J Am Diet Assoc 2002;102:1648–51.

22 Liu T, Howard RM, Mancini AJ, Weston WL, Paller AS, Drolet BA, Esterly NB, Levy ML, Schachner L, Frieden IJ. Kwashiorkor in the United States: fad diets, perceived and true milk allergy, and nutritional ignorance. Arch Dermatol. 2001;137(5):630–6.

23 George D, Wasko C, Metry D. Atopic dermatitis and nutritional rickets: an exercise in parental counseling. Pediatr Dermatol. 2006;23(1):102–3.

24 Paganus A, Juntunen-Backman K, Savilahti E. Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatr. 1992;81(6–7):518–21.

25 Isolauri E, Sütas Y, Salo MK, Isosomppi R, Kaila M. Elimination diet in cow's milk allergy: risk for impaired growth in young children. J Pediatr. 1998;132(6):1004–9.

26 Sampson HA. The evaluation and management of food allergy in atopic dermatitis. Clin Dermatol 2003;21:183–92.

27 Pike MG, Chang CL, Atherton DJ, Carpenter RG, Preece MA. Growth in atopic eczema: a controlled study by questionnaire. Arch Dis Child. 1989;64(11):1566–9.

28 Kristmundsdottir F, David TJ. Growth impairment in children with atopic eczema. J R Soc Med. 1987;80(1):9–12.

29 Patel L, Clayton PE, Jenney ME, Ferguson JE, David TJ. Adult height in patients with childhood onset atopic dermatitis. Arch Dis Child. 1997;76(6):505–8.

30 Fox AT, Du TG, Lang A, Lack G. Food allergy as a risk factor for nutritional rickets. Pediatr Allergy Immunol 2004;15:566–9.

31 Carvalho NF, Kenney RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. Pediatrics 2001;107:E46.

32 Davidovits M, Levy Y, Avramovitz T, Eisenstein B. Calcium-deficiency rickets in a four-year-old boy with milk allergy. J Pediatr. 1993;122(2):249–51.

33 Levy Y, Davidovits M. Nutritional rickets in children with cow's milk allergy: calcium deficiency or vitamin D deficiency? Pediatr Allergy Immunol. 2005;16(6):553.

34 Lawson M, Thomas M. Vitamin D concentrations in Asian children aged 2 years living in England: population survey. BMJ 1999;318:28.

35 Heldenberg D, Tenenbaum G, Weisman Y. Effect of iron on serum 25-hydroxyvitamin D and 24, 25-di-hydroxyvitamin D concentrations. Am J Clin Nutr 1992;56:533–6.

36 Wharton B, Bishop N. Rickets. Lancet 2003;362:1389–400.

37 Jensen VB, Jørgensen IM, Rasmussen KB, Mølgaard C, Prahl P. Bone mineral status in children with cow milk allergy. Pediatr Allergy Immunol. 2004;15(6):562–5.

38 Konstantynowicz J, Nguyen TV, Kaczmarski M, Jamiolkowski J, Piotrowska-Jastrzebska J, Seeman E. Fractures during growth: potential role of a milk-free diet. Osteoporos Int 2007;18(12):1601–7.

39 Ladoyanni E, Cheung ST, North J, Tan CY. Pellagra occurring in a patient with atopic dermatitis and food allergy. J Eur Acad Dermatol Venereol 2007;21(3):394–6.

40 Des Roches A, Paradis L, Paradis J, Singer S. Food allergy as a new risk factor for scurvy. Allergy 2006;61(12):1487–8.

41 Carvalho NF, Kenney RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. Pediatrics 2001;107:E46.

42 MacDonald A, Forsyth A. Nutritional deficiencies and the skin. Clin Exp Dermatol. 2005;30(4):388–90.

43 Roesler TA, Barry PC, Bock SA. Factitious food allergy and failure to thrive. Arch Pediatr Adolesc Med. 1994;148(11):1150–5.

44 Pugliese MT, Weyman-Daum M, Moses N, Lifshitz F. Parental health beliefs as a cause of nonorganic failure to thrive. Pediatrics. 1987;80(2):175–82.

45 Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M, King RM, Roberts G, Lucas JS. Management of nut allergy influences quality of life and anxiety in children and their mothers. Pediatr Allergy Immunol 2010 Jan 14;[In press]

46 Smith MM, Lifshitz F. Excess fruit juice consumption as a contributing factor in nonorganic failure to thrive. Pediatrics. 1994;93(3):438–43.

47 Cantani A, Micera M. Immunogenicity of hydrolysate formulas in children (Part 2): 41 case reports. J Investig Allergol Clin Immunol 2001;11(1):21–6.

48 5825 Caffarelli C, Plebani A, Poiesi C, et al. Determination of allergenicity to three cow's milk hydrolysates and an amino acid-derived formula in children with cow's milk allergy. Clin Exp Allergy 2002;32:74–9.

49 American Academy of Pediatrics. Committee on Nutrition. Soya protein-based formulas: recommendations for use in infant feeding. Pediatrics 1998;101:148–53.

50 Savino F, Castagno E, Monti G, et al. Z-score of weight for age of infants with atopic dermatitis and cow's milk allergy fed with a rice-hydrolysate formula during the first two years of life. Acta Paediatr Suppl 2005;94:115–9.

51 Restani P, Beretta B, Fiocchi A, Ballabio C, Galli CL. Cross-reactivity between mammalian proteins. Ann Allergy Asthma Immunol 2002:6(Suppl. 1):11–5.

52 Restani P, Gaiaschi A, Plebani A, et al. Cross-reactivity between milk proteins from different animal species. Clin Exp Allergy 1999;29:997–1004.

53 Bellioni-Businco B, Paganelli R, Lucenti P, et al. Allergenicity of goat's milk in children with cow's milk allergy. J Allergy Clin Immunol 1999;103(6):1191–4.

54 Tavares B, Pereira C, Rodrigues F, Loureiro G, Chieira C. Goat's milk allergy. Allergol Immunopathol (Madr) 2007;35(3):113–6.

55 Du Toit G, Weinberg EG. Use of goat's milk in cow's milk-allergic infants. S Afr Med J. 2002;92(1):49.

56 Paty E, Chedevergne F, Scheinmann P, Wal J-M, Bernard H. Allergy to goat's milk and sheep's milk without allergy to cow's milk. Revue francaise d allergologie 2003;43(7):455–62.

57 Infante Pina D, Tormo Carnice R, Conde Zandueta M. Use of goat's milk in patients with cow's milk allergy. [Spanish] An Pediatr (Barc). 2003;59(2):138–42.

58 Santangelo, CM, McCloud, E. Nutritional management of children who have food allergies and eosinophilic esophagitis. Immunol Allergy Clin North Am 2009;29:77.

59 Novak-Wegrzyn A. Food protein induced enterocolitis, enteropathy and proctocolitis. In: Sampson H, Metcalfe D, Simon R, eds. Food Allergy. Adverse Reactions to Foods and Food Additives, 3rd Edn. Cambridge, MA: Blackwell Scientific Publications, 2003:232–4.

60 Guajardo J, Rothenberg M. Eosinophilic esophagitis, gastroenteritis, gastroenterocolitis and colitis. In: Sampson H, Metcalfe D, Simon R, eds. Food Allergy. Adverse Reactions to Foods and Food Additives, 3rd Edn. Cambridge, MA: Blackwell Scientific Publications, 2003:217–23.

61 Hill DJ, Cameron DJ, Francis DE, Gonzalez-Andaya AM, Hosking CS. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. J Allergy Clin Immunol. 1995;96(3):386–94.

62 Sampson HA, James JM, Bernhisel-Broadbent J. Safety of an amino acid-derived infant formula in children allergic to cow milk. Pediatrics 1992;90:463–5.

63 Vanderhoof JA, Murray ND, Kaufman SS, Mack DR, Antonson DL, Corkins MR, Perry D, Kruger R. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. J Pediatr. 1997;131(5):741–4.

64 De Boissieu D, Matarazzo P, Dupont C. Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula. J Pediatr. 1997;131(5):744–7.

65 Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin Exp Allergy. 2007;37(6):808–22.

66 Hon KL, Leung TF, Kam WY, Lam MC, Fok TF, Ng PC. Dietary restriction and supplementation in children with atopic eczema. Clin Exp Dermatol. 2006;31(2):187–91.

67 McGough N, Cummings JH. Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye. Proc Nutr Soc 2005;64(4):434–50.

68 Fujimoto W, Inaoki M, Fukui T, Inoue Y, Kuhara T. Biotin deficiency in an infant fed with amino acid formula. J Dermatol. 2005;32(4):256–61.

69 Mamada Y, Murata T, Taniguchi A, Hasegawa Y, Suzuki T, Kohda K, Nasuno K, Watanabe T, Yamaguchi S, Ishiguro A. Biotin deficiency in amino acid formula nutrition for an infant with milk protein allergy. [Japanese] Arerugi. 2008;57(5):552–7.

70 Higuchi R, Noda E, Koyama Y, Shirai T, Horino A, Juri T, Koike M. Biotin deficiency in an infant fed with amino acid formula and hypoallergenic rice. Acta Paediatr. 1996;85(7):872–4.

71 Senna G, Passalacqua G, Lombardi C, Antonicelli L. Position paper: controversial and unproven diagnostic procedures for food allergy. Allerg Immunol. 2004;36(4):139–45.

72 Niggemann B, Gruber C Unproven diagnostic procedures in IgE-mediated allergic diseases. Allergy 2004;59(8):806–8.

73 Allergy Society of South Africa. ALCAT and IgG allergy and intolerance tests. S Afr Med J. 2008;98(3):167.

74 Warner JO. The UK allergy paradox. Pediatr Allergy Immunol 2004;15:287–8.

75 Senna G, Bonadonna P, Schiappoli M, Leo G, Lombardi C, Passalacqua G. Pattern of use and diagnostic value of complementary/alternative tests for adverse reactions to food. Allergy 2005;60:1216–7.

76 Rosenthal M. How a non-allergist survives an allergy clinic. Arch Dis Child 2004;89:238–43.

77 Foote KD, Marriott LD. Weaning of infants. Arch Dis Child 2003;88:488–92.

78 Koletzko S, Koletzko B. Allergen avoidance approaches in food allergy management. Nestle Nutr Workshop Ser Pediatr Program. 2009;64:169–80; discussion 180–4, 251–7.

Causes and management of diarrhoea in children in a clinical setting

Cooke ML
Department of Paediatrics and Child Health, Stellenbosch University
Correspondence to: Dr M Cooke, e-mail: lcooke@sun.ac.za

Abstract

Diarrhoeal disease and its complications remain a major cause of morbidity and mortality in children, especially in developing countries. Diarrhoea is characterised by an increased frequency and volume, and decreased consistency of stool from the norm. Pathogens vary between developed and developing world settings. Rotavirus diarrhoea is the most important aetiological agent implicated in severe dehydrating diarrhoea. Although it is important to recognise the specific microbiological causation of diarrhoea in order to target appropriate treatment, the broader preventive aspects put forward by the World Health Organization (WHO) indicate the fundamental contributors to the massive burden of disease in developing countries. The management of a child presenting with acute diarrhoea must include a thorough history and examination with evaluation of hydration status, nutritional status and comprehensive clinical evaluation for any complications or associated illnesses. The most recent advances in the area of acute diarrhoeal disease include zinc supplementation, reduced osmolarity oral rehydration solution (ORS) and rotavirus vaccination.

S Afr J Clin Nutr 2010;23(1) Supplement:S42-S46

Diarrhoeal disease and its complications remain a major cause of morbidity and mortality in children, especially in developing countries. It is the second most common cause of death in children under five years of age worldwide and is responsible for 2.4 million deaths each year.[1] The Medical Research Council Burden of Disease report indicates that in South Africa, it is the third biggest killer of children under five, responsible for over 10 000 deaths annually(10.2% of total deaths).[2] There are approximately 1.5 billion episodes of diarrhoea per year so knowledge of aetiology and appropriate management is essential for all health care practitioners. The most recent advances in the area of acute diarrhoeal disease include zinc supplementation, reduced osmolarity oral rehydration solution (ORS) and rotavirus vaccination.

Definitions

Diarrhoea is characterised by an increased frequency and volume, and decreased consistency of stool from the norm. It must be remembered that frequency of passing stool varies with age and is higher in infants.[4] Dysentery is defined as the passage of blood and mucous in diarrhoeal stools. Persistent diarrhoea occurs when the duration of symptoms exceeds seven days and chronic diarrhoea when it lasts more than 14 days.[4,5]

Causes of diarrhoea

The commonest causes of infectious diarrhoea are shown in Table I.

The incidence of these pathogens varies between developed and developing world settings. In developed countries about 70% of diarrhoea cases are of viral (40% rotavirus),10–20% of bacterial and < 10% of protozoal origin.[3.5.6,7] In developing countries 50–60% of cases are of bacterial (Enteropathogenic *E. Coli* 25%, *Campylobacter jejuni* 10–18%, *Shigella* spp and *Salmonella* spp 5% each), 35% of viral(15–25% rotavirus) origin, and in many the cause is unidentified or mixed.[3.5.6,7,8] In developing countries the prevalence of diarrhoea also varies widely by country. For instance, there are many more

Table I: Common pathogens causing childhood diarrhoea

Viruses
- Rotavirus
- Norovirus
- Enteric adenovirus
- Other: caliciviruses, astroviruses, enteroviruses

Bacteria
- *Campylobacter jejuni*
- Non-typhoid *Salmonella* sp
- Enteropathogenic *E. Coli*
- *Shigella* spp
- *Salmonella typhi*
- Shiga-toxin producing *E. Coli* (ETEC)
- *Vibrio cholera*

Protozoa
- Cryptosporidium parvum
- *Giardia lamblia*
- Entamoeba histolytica

Unidentified

Mixed infections

cases of cholera in India and South east Asia, whilst in Africa rotavirus has been shown to be the causative agent in 28-49% of cases in Ethiopia but only 14 % of cases in Tanzania.[7,8] The incidence of rotavirus diarrhoea varies widely even within each country with studies from South Africa indicating a range of 14–34% of cases in Johannesberg, 20–55% in Durban[7] and 18% in Cape Town.[9]

There is also a marked seasonality that is associated with the incidence of infectious childhood diarrhoea. This is best reflected in rotavirus infection, classically described in dry winter months in temperate climates.[5,7,8] This is documented in studies from Durban and Johannesberg, but not in the summer peak of diarrhoea in Cape Town and other developing countries.[7,9] This pattern is most likely due to the Mediterranean climate in Cape Town with wet winters and hot dry summers.

Bacterial pathogens like *Campylobacter jejuni* and *Salmonella* spp invade the lining of the small and large intestine and trigger inflammation so children tend to have higher fevers and a dysentery-like picture. These organisms can spread systemically especially in young children. *Shigella dysenteriae* and ETEC infections can also be complicated by the haemolytic uraemic syndrome.[5]

Certain organisms are more closely associated with chronic diarrhoea, and these include *Giardia lamblia* and *Cryptosporidium parvum*.[3]

Rotavirus diarrhoea is the most important aetiological agent worldwide implicated in severe dehydrating diarrhoea requiring hospitalisation. The annual burden of disease is estimated as more than 110 million diarrhoeal episodes, 25 million clinic visits, 2 million hospitalisations and 600 000 childhood deaths per year.[7,8,10,11] More than 90% of rotavirus deaths occur in developing countries. Improvements in water supply and sanitation have been shown to reduce the transmission of enteric bacteria and parasites, but do not appear to have a major impact on rotavirus diarrhoea, so the introduction of a vaccine shows the greatest promise in reducing the burden of disease. The peak age of infection is quoted as six months to two years. In developing countries, however, children often present younger, with the median age of hospitalisation of all-cause diarrhoea being nine months when compared with that of six months in rotavirus diarrhoea, with 97% of cases occurring in children younger than 18 months. Some studies indicate that up to 38% of patients with rotavirus diarrhoea were < 6 months of age. A small infectious dose is required (< 100 virus particles) for the virus to enter the small intestinal epithelium where it elaborates a potent enterotoxin which damages epithelial cells causing blunted villi and massive viral shedding. This results in a profuse watery non-inflammatory diarrhoea, rapid dehydration and electrolyte disturbances. It is often associated with initial fever and vomiting for two to three days, and the course of the infection lasts two to seven days.[8,10,11]

The recent outbreak of cholera in Zimbabwe with rice-water stools and rapid dehydration, has highlighted the risks of the spread and severity of illness. A travel history is important when considering the aetiology of diarrhoea as management may differ, including the need for isolation and notification.[3] When a child presents with diarrhoea, especially in chronic non-dehydrating diarrhoea, *noninfectious causes* must also always be considered in the differential diagnosis[5] (Table II).

Table II: Differential diagnosis in children presenting with diarrhoea

- Infections outside the GIT, like meningitis and urinary tract infection
- Surgical conditions like intussuseption and malrotation, especially if prominent/bile-stained vomiting is present
- Immunodeficiency e.g. HIV disease
- Spurious diarrhoea – faecal impaction with overflow
- Side-effects of medications e.g. antibiotics
- Primary gastrointestinal tract pathology e.g. cystic fibrosis, inflammatory bowel disease, coeliac disease
- Toddler's diarrhoea

GIT = Gastrointestinal tract

The aetiologic approach in *nosocomial diarrhoea* will also differ as one needs to consider *Clostridium difficile* infection. This is a spore forming anaerobe, and patients colonised with a toxin producing strain can develop disease especially when treated with antibiotics. Rotavirus and astrovirus are other important causes of nosocomial diarrhoea outbreaks through the faecal-oral transmission and contamination of environmental surfaces.[3]

Although it is important to recognise the specific microbiological causation of diarrhoea in order to target appropriate treatment, the broader preventive aspects put forward by the WHO indicate the fundamental contributors to the massive burden of disease in developing countries. In a global setting where up to a quarter of children are malnourished, over a billion people do not have access to safe water and over two billion have inadequate sanitation, together with a low breastfeeding prevalence, social disruption from war and natural disasters as well as poor maternal education, the vicious cycle of infection, diarrhoea and malnutrition is perpetuated.[3]

Management

Management of a child presenting with acute diarrhoea must include a thorough history and examination with evaluation of hydration status, nutritional status and comprehensive clinical evaluation for any complications or associated illnesses.[4,5] A decision then needs to be made on method of rehydration, feeding, and if there are indications for any specialised investigations. Pharmacologic therapy is usually limited to micronutrient support.[4,5]

Clinical evaluation

After obtaining a history of diarrhoea with or without vomiting, the first priority in initial evaluation is to identify and treat shock. The clinical features and initial management of shock are shown in Table III. These children require rapid venous access, and after the initial fluid bolus, a 10 ml/kg bolus should be repeated if signs of shock persist. Such children may also need additional general supportive care including oxygen and must be continuously and very intensively monitored.[5,12]

Table III: Features and management of shock and dehydration (modified from WHO and IMCI)[4,5]

No visible dehydration	Some dehydration	Severe dehydration	Shock
Features: • alert with normal eyes • not thirsty • normal skin pinch	2 or more signs: • restless and irritable • thirsty and drinks eagerly • skin pinch returns slowly • fontanelle is sunken	2 or more signs: • lethargic or sleepy • deeply sunken eyes and fontanelle • very slow skin pinch	**Signs of:** • depressed level of consciousness or weakness • weak or absent peripheral pulses • a prolonged capillary refill time of > 3 seconds • tachycardia of > 120 bpm Usually but not always with evidence of severe extravascular dehydration
Initial fluid management • treated at home with additional fluids • Other supportive measures	• ORS orally or nasogastrically • Continue breastfeeding or formula milk within 4 hours • Replace ongoing losses with ORS	• Intravenous rehydration with ½ Darrows Dextrose • Continue breastfeeding or formula within 4 hours • Replace ongoing losses with ORS	• Rapid venous access, either an intravenous or intraosseous line • Bolus of 20 ml/kg of Ringers lactate or Normal Saline.

ORS = Oral Rehydration Solution

Further history should include information on the duration and frequency of diarrhoea, presence of blood or mucous in the stool, vomiting and whether it is bile stained, use and mixing of home rehydration fluids, as well as other usual aspects of the paediatric history including past illnesses, immunisation status, feeding, medications and related side effects. The Integrated Management of Childhood Illness (IMCI) has simplified the classification dehydration into i) no signs of dehydration, ii) some dehydration (correlating with the old classification of 5% dehydration), and iii) severe dehydration (correlating with the old classification of 10% dehydration)[12] (Table III), The indications for hospitalising a child with diarrhoea are shown in table IV.

Table IV: Indications for hospitalisation[4,5]

- Severe dehydration with/without shock
- Altered neurological status
- Intractable vomiting or ORS failure
- Caregivers that cannot provide adequate care at home
- Young age, < 6 months with dehydration
- Children with associated chronic illness
- Enteric fever: high fever with inflammatory diarrhoea
- Dysentery especially < 1 year (IMCI)*
- Tender abdomen and any suspected surgical condition
- High output diarrhoea
- Persistent diarrhoea

* IMCI = Integrated Management of Childhood Illness

A relatively objective way of assessing dehydration is comparing current weight with a recently recorded weight, usually in the Road to Health Card (RTHC) to calculate the percentage dehydration. Capillary refill time, skin turgor and an abnormal respiratory pattern indicative of acidosis have been found by systematic review to be the best indicators of degree of dehydration.[3,5]

Rehydration and fluid management

The observation that glucose-sodium co-transport was unaffected in cholera and recognition that secretory and absorptive processes in the intestine are separate, led to the formulation of Oral Rehydration Solution (ORS), with similar concentrations of sodium and glucose that optimise absorption together with potassium, chloride and bicarbonate.[3] It is considered one of the most important medical innovations of modern times and its active promotion as part of the WHO Control Diarrheal Disease (CDD) programme in the 1980s halved the deaths from diarrhoea over 20 years following its implementation.[1,7]

A Cochrane review has documented that oral rehydration should be used as the first line for management of children with acute gastroenteritis and some dehydration.[13] When this is not feasible, enteral rehydration by nasogastric route is as effective, if not better, than IV rehydration (Table V), with fewer major adverse events and shorter hospital stay. In addition, it is cheaper in terms of both consumables and human resources and less traumatic for the child.[4,5,13]

Table V: Indications for intravenous fluids

- Shock
- Severe dehydration, especially if depressed level of consciousness
- Paralytic ileus
- Moderate dehydration with vomiting all fluid
- Children with profuse watery stools unable to keep up with fluid losses

Note: Intravenous fluids should be avoided in children who are malnourished or with underlying cardiac or respiratory disease including associated pneumonia.

The WHO, European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and American Academy of Paediatrics(AAP) all recommend rapid rehydration over four hours in mild to moderate(IMCI "some") dehydration. Rehydration should be slower over 8–24 hours in children under three months of age, those with respiratory or cardiac disease, those with suspected or proven hypernatraemia and in malnourished children.[13]

There has been ongoing controversy regarding the ideal composition of ORS. Initial WHO preparations had higher sodium concentration due to its development in areas with high incidence of cholera (which is complicated by hyponatraemia). After multiple modifications the current WHO Guidelines recommend a *reduced osmolarity ORS* with lower concentrations of sodium (75 mmol/l vs 90 mmol/l) and glucose (75 mmol/l vs 111 mmol/). A meta-analysis has shown its safety and efficacy in both cholera and non-cholera diarrhoea, with lower use

of intravenous fluid rescue, reduced vomiting and similar rates of hyponatraemia when reduced osmolarity is compared with standard ORS.[3,4,5] ESPGHAN in fact recommends an even lower concentration of sodium of 60 mmol/l for use in children with diarrhoea in Europe due to the different aetiology of diarrhoea in European settings.[4]

Multiple other modified formulations of ORS have also been extensively studied. Rice-based ORS can be used as an alternative therapy to standard ORS in cholera, as it adds additional substrate to the gut lumen without increasing osmolality, thereby providing additional glucose molecules for glucose-mediated absorption. However, there is no additional benefit in children with non-cholera diarrhoea. Other modifications include ORS-containing amylase-resistant starch, as it is postulated that the non-absorbed carbohydrates increase short-chain fatty acids availability which enhance colonic absorption of sodium and water, but further trials are needed to demonstrate superiority. ORS has also been combined with guar gum, a mixture of non-digestible carbohydrates, as well as with probiotics, zinc and glutamine but there is currently insufficient evidence for any of their use bearing in mind the additional considerations of increased cost, instability and availability of additional compounds.[4]

Prevention of further dehydration by supplementing maintenance fluid with ORS with each loose stool to replace ongoing loses is an essential part of further management (50–100ml per loose stool). The child's hydration status must be re-assessed regularly at least every four to six hours including a weight check, and fluids modified according to whether there is improvement or not.[5]

Maintain nutrition

Consensus from WHO, ESPGHAN and the AAP based on level 1 evidence is to continue breastfeeding at all times, and to continue normal feeds in uncomplicated gastroenteritis within four hours. There is no role for dilution or gradual re-introduction of formula or for special formulae like soya-based or lactose free. Beverages with high sugar content should not be used. An extra meal a day for at least a week following an episode of gastroenteritis should also be encouraged to allow catch-up growth[4,5,13].

Investigations

Testing for electrolytes should be performed on hospitalised children with severe dehydration or shock, those receiving intravenous fluids, those with associated malnutrition and in any child that looks ill out of proportion to their degree of dehydration.[4,5] Children appearing floppy or with abdominal distension must have hypokalaemia excluded, and hypernatraemia should be suspected in well-nourished children, with a rubbery feel to the skin, those with a high pitched cry, and in any children with a history of incorrect mixing of ORS. Indications for sending a stool microscopy, culture and sensitivity (MCS) include inflammatory diarrhoea with blood and pus in the stool, high fever and systemic illness, persistent diarrhoea and in hospitalised children that develop diarrhoea, including for *C. difficile*. Routine testing for rotavirus is of epidemiologic interest but does not change the management of diarrhoea which is supportive. Most laboratories do not test for *E. Coli* types so the yield from stool MCS is low, and routine stool testing is not recommended.[3,4,5]

There is no role for routine full blood count and inflammatory markers like C-reactive protein in uncomplicated gastroenteritis but young children under three months and children with a high fever should have a formal septic workup.[3,4,5]

Pharmacologic therapy

Zinc deficiency is common in young children in the developing world and is associated with impaired electrolyte and water absorption, decreased brush border enzyme activity and impaired cellular and humoral immunity. Meta-analyses have confirmed that zinc supplementation reduces the duration and severity of acute and persistent diarrhoea and reduces the risk of a recurrent episode in the next 2–3 months. WHO and UNICEF recommend zinc supplementation (10 mg in children under six months and 20 mg in children over six months) for 10–14days as a universal treatment.[14,15,16] ESPGHAN however does not recommend it as a routine treatment modality in European children, unless they are malnourished.[4]

Probiotics may be an effective adjunct to the management of diarrhoea, but it is important to prescribe those that have been documented to be effective. *Lactobacillus GG* and *Saccharomyces boulardii* have the most consistently documented efficacy data. Best results have been demonstrated in young infants with viral gastroenteritis when the probiotic is administered early in the course of the diarrhoea, at a dose of 10^{10} CFU/day. The advantages include reduced duration of diarrhoea by one day thereby reducing costs of hospitalisation, reduced persistent diarrhoea and reduced spead through viral shedding. There are concerns however in the developing world regarding the use of probiotics in the management of diarrhoea because of the high prevalence of bacterial diarrhoea in such clinical settings, in which probiotcs may be less efficacious and safety issues related to immunosuppression may arise.[4,16]

Management of diarrhoea is otherwise usually supportive and non-pharmacologic. Antimotility agents like loperamide have been associated with prolonged disease in Shigellosis, toxic megacolon in *C. difficile* infection, and haemolytic-uraemic syndrome in children with Shiga-toxin producing *E. Coli* and are not recommended.[3,4,5]. The older anti-emtics are also not recommended due to risk of extra-pyramidal side-effects but some newer agents like ondansetron are effective without side-effects.[4,5] There is no evidence to support the use of prebiotics, glutamine, folic acid, kaolin-pectin, attapulgite, activated charcoal or bismuth. There may however be potential benefit in the use of smectite, an aluminmagnesium silicate that binds digestive mucous.[4] Vitamin A does not influence the course of acute diarrhoea but should be given according to national guidelines for its effect on reducing overall mortality.[4] Antibiotics are not routinely recommended in viral or uncomplicated bacterial gastroenteritis (Table VI).

Table VI: Indications for systemic antibiotics.

Indications	Antibiotic regimen
• Bacterial gastroenteritis complicated by sepsis • Neonates • Ill immunocompromised children • Associated infection e.g. urinary tract infection or pneumonia	• Usually ampicillin and gentamicin OR ceftriaxone
Dysentery • *Shigella* • *Salmonella* spp (non-typhoid)	• Nalidixic acid, fluoroquinolone or ceftriaxone
• *Campylobacter* First try to exclude ETEC due to the associated with HUS	• Erythromycin or one of above
Specific infections:	
• Amoebiasis	• Metronidazole
• Giardiasis	• Metronidazole
• *Vibrio cholera* if complicated by severe dehydration	• Doxycycline(> 6 years) or fluoroquinolone
• *C. difficile*	• Metronidazole or oral vancomycin

ETEC = Enterotoxigenic *E. Coli*, HUS = Haemolytic Uraemic Syndrome

Management of children with chronic diarrhoea

As for the child presenting with acute diarrhoea, there should be a thorough history, including family history, and comprehensive clinical evaluation including effect on nutritional status for those with chronic diarrhoea.[17] It is important to differentiate whether this is a persistent diarrhoea following an acute dehydrating diarrhoeal episode, as causes may include small bowel bacterial overgrowth, acquired disaccharidase deficiency, deconjugation and dehydroxylation of bile salts which induces diarrhoea, protein sensitisation i.e clinical settings that may require additional specialised treatment.[18] The clinical picture of the child is also of importance since it may be indicative of the cause of diarrhoea such as the classic Toddler's Diarrhoea with a thriving child and stools containing undigested food and worsening as the day progresses. The need for any specialised investigation and treatment will depend on the clinical picture of the patient and would usually include stool MC&S to exclude parasites, stool reducing substances and elastase, and possibly sweat test or coeliac serology.[17]

Prevention

On discharge of a child with an episode of diarrhoea, advice must be given on measures to try to prevent another episode and appropriate home management to prevent dehydration.

The WHO Enhanced Diarrhoeal Disease Control (EDDC) focuses on a combination of public health issues like handwashing, preparation and storage of food as well as drinking water and sanitation; promotion of breastfeeding (which affords a six-fold protection); zinc supplementation and rotavirus vaccines.[1] The enormous burden of rotavirus disease has been mentioned and vaccine introduction in developing countries is thought to have the potential to save 600 000 children's lives per year and help towards the achievement of the Millenium Development Goal of reducing childhood mortality by 2/3 by 2015.[1,8] Rotarix has been licensed in South Africa since 2006 and was introduced in the Extended Programme of Immunisation in 2009. It is a live attenuated human rotavirus strain, with two doses given orally foour weeks apart, not after six months. In studies in middle-income countries the vaccine has a very good safety profile and efficacy of 85% protection. There are some concerns though about its use in the developing world. Such concerns include interference by high titres of maternal antibodies, interference by gut microorganisms as well as safety and immunogenicity in HIV-infected children. Nevertheless, the vaccine holds promise as an extremely important and much needed public health intervention to reduce the significant morbidity and mortality from diarrhoeal disease.[8,10,11]

References

1. Forsberg BC, Petzold MG, et al. Diarrhoea case management in low-and middle-income countries –an unfinished agenda. Bulletin of the WHO Jan 2007,85(1).
2. Burden of Disease report, Medical Research Council (MRC). http://www.mrc.ac.za/policybriefs/childmortality.pdf Accessed 27 January 2010.
3. Cheng AC, McDonald JR, Thielman NM. Infectious Diarrhoea in Developed and Developing Countries. J Clin Gastroenterol 2005;39(9):757–73.
4. Guarino A, Albano F, Ashkenazi S, et al. European Society for Paediatric Gastroenetrology, hepatology and Nutrition/European Society for paediatric Infectious Diseases Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe. JPGN 2008; 46:S81–S122.
5. Elliott EJ. Acute Gastroenteritis in Children. BMJ 2007;334:35–40.
6. Wilson ME. Diarrhea in Nontravelers: Risk and Etiology. CID 2005:41(suppl 8):S541–S546.
7. Cunliffe NA, Kilgore PE, Bresee JS, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. Bulletin of the World Health Organisation 1998;76(5):525–37.
8. Naghipour M, Nakgomi T, Nakagomi O. Issues with reducing the rotavirus-associated mortality by vaccination in developing countries. Vaccine 2008;26:3236–41.
9. Househam KC, Mann MD, Bowie MD. Enteropathogens associated with acute infantile diarrhoea in Cape Town. S Afr Med J 1988;73:83–7.
10. Glass RI, Parashar UD et al. Rotavirus vaccines: current prospects and future challenges. Lancet 2006;368:323–32.
11. Dennehy PH. Rotavirus vaccines: an update. Vaccine (2007), doi:10.1016/j.
12. http://www.who.int/child_adolescent_health/topics/prevention_care/child/imci/en/index.html Accessed 27 January 2010.
13. Bellemare S, Hartling L et al. Oral rehydration versus intravenous therapy for treating dehydration due to gastroenteritis in children: a meta-analysis of randomised controlled trials. The Cochrane Library 2006, issue 4.
14. Hoque KM, Binder HJ. Zinc in the Treatment of Acute Diarrhoea: Current Status and Assessment. Gastroenterol 2006;130:2201–5.
15. A Meta-analysis of the Effects of Oral Zinc in the Treatment of Acute and Persistent Diarrhea. Pediatrics 2008;121(2):326–36.
16. Salvatore S, Hauser B, Devreker T, et al. Probiotics and zinc in acute infectious gastroenteritis in children: are they effective? Nutrition 2007;23:498–506.
17. Wittenberg DF ed. Gastrointestinal Disorders in Coovadia's Paediatrics and Child Health(6th edition) 2009:501–17.
18. Bhutta ZA, Nelson EA, Lee WS, et al. Recent Advances and Evidence Gaps in Persistent Diarrhea. JPGN 2008;47:260–5.

The metabolic syndrome – What is the value of its identification?

Till A, RD (SA)
Author to provide affiliation
Correspondence to: Me Anne Till, e-mail: anne@annetill.co.za

Abstract

The identification of the metabolic syndrome (MS) has been under discussion and intense investigation since 1998. Only recently does it appear that consensus is being reached between different organisations regarding its identification. Nonetheless, the true value in identifying the MS remains under question, as does the debate around its existence. The real value in identifying the MS may simply be the ability to identify individuals at increased risk for developing cardiovascular disease (CVD) and diabetes. Further identification of abnormalities associated with the MS should encourage practitioners to investigate and search for other risk factors associated with CVD and diabetes. Part of the problem in identifying and treating the MS is that the cause of associated abnormalities remains unclear. However current research seems to indicate that oxidative stress and inflammation may play a pivotal role in the development of insulin resistance (IR) and the MS. Regardless of the usefulness of indentifying the MS and its contributing causes, certain take home messages for practitioners remain the same, including emphasis on the importance of weight loss in overweight patients, the role of regular exercise and diet quality, with a new emphasis on the role of an adequate micronutrient intake and specifically nutrients with antioxidant properties..

S Afr J Clin Nutr 2010;23(1) Supplement:S47-S49

The evolution of the concept of the metabolic syndrome

It was in the late 1980s and early 1990s that Gerald Reaven proposed that a clustering of abnormalities including increased plasma triglyceride (Tgs) levels, decreased high density lipoprotein-cholesterol (HDL-C) concentration and high blood pressure (BP) linked to decreased insulin mediated glucose uptake and impaired glucose tolerance (IGT) comprised a syndrome.[1] In 1998, the first formalised definition of the metabolic syndrome (MS) was proposed by a World Health Organization consultation group. The diagnosis of MS by the WHO criteria required evidence of insulin resistance (IR) for diagnosis.[2] It was subsequently pointed out by a position statement generated by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) task force, which was set up to provide guidance to clinicians on the identification and treatment of the MS, that the identification of IR in practice is not accurate due to the lack of standardised methods used to quantify plasma insulin concentrations in a laboratory setting. They stated that there is no evidence to support an individual being defined as insulin resistant, and at increased risk of developing any of the abnormalities of the MS, on the basis of plasma insulin concentrations alone. The AACE/ACE task force strongly cautioned practitioners against trying to identify individuals as IR, by making use of laboratory tests to identify fasting plasma insulin levels, in order to calculate a fasting insulin:glucose ratio (FIGR) as a surrogate marker of IR.[3]

After the WHO criteria, other criteria came from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001. ATP III did not require the identification of IR as part of the criteria for diagnosis of the MS. The ATP III criteria made the presence of three of the following five features the basis for recognition of the MS: abdominal obesity (highly correlated with IR), elevated Tgs, reduced HDL-C, elevated BP, and elevated fasting glucose (impaired fasting glucose or type 2 diabetes mellitus).[4] MS is a predictor of CVD and diabetes. When CVD or diabetes develops, the MS is often present, and the number of components of the MS contributes to increased disease risk and disease progression.[2] In 2005, the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to address differences in the definitions of the MS.[5,6] However, differences remained with regard to separate recommendations relating to waist circumference cut off points. The IDF did not require the WHO criteria of insulin resistance for diagnosis, but made abdominal obesity necessary as one of five factors (Table I) required in the identification of MS, while highlighting waist circumference measurements as a useful screening tool; the remainder of the criteria were the same as those set by ATP III.[2] The AHA/NHLBI slightly adjusted the ATP III criteria but did not make waist circumference measurements and implied abdominal obesity a required criteria for diagnosis. The remaining four criteria were the same as defined by the IDF.[6] There was, however, no agreement on the cut points for waist circumference measurements and abdominal obesity between the IDF and AHA/NHLBI. The IDF recommended a threshold for waist circumference measurements to be defined for people of European origin (Europids) to be 94 cm for men and 80 cm for women; the AHA/NHLBI, recommended cut points of 102 and 88 cm, respectively.[2]

Is it worthwhile identifying people with MS?

Much time and effort have gone into trying to establish uniform criteria for the identification of the MS. Yet controversy still exists around

the true value of identifying the MS. A recent scientific statement by the IDF, NHBLI, AHA, the World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity states that the MS is a complex of interrelated risk factors for CVD and diabetes, and that the MS is widespread and has an increasing incidence worldwide which relates mostly to the increased prevalence of obesity and sedentary living.[2] Further, a syndrome is merely a clustering of factors for which the cause is uncertain, and these factors occur simultaneously more often than by chance alone.[2] The MS does not determine absolute risk [it does not contain factors that determine entire risk such as other risk assessment tools, for example the Framingham 10 Year risk factor analysis for CVD, such as age, gender, smoking, total or low density lipoprotein cholesterol levels (LDL-C)][2,10]. However, according to Alberti et al, patients with the MS have double the risk of developing CVD over five to ten years when compared with individuals who do not have the syndrome. The risk over a lifetime is most probably even greater.[2] In addition, the MS confers a fivefold increase in risk for type 2 diabetes.[2]

It appears therefore that the primary merit in identifying individuals with the MS is to identify risk for the development of CVD and diabetes[2] and that perhaps the other value of the syndrome as a concept is the obvious utility that the identification of one of the CVD risk factors in a patient should prompt search for other risk factors.[7,10]

It is also worthwhile noting that the criteria used for the identification of the MS is far from finite, there are many other signs and symptoms that are associated with IR and the MS, including, but not limited to, albuminuria, a prothrombotic and pro-inflammatory state [plasminogen activator inhibitor-1 and fibrinogen, elevated C-reactive protein (CRP), Tumour Necrosis Factor-α (TNFα), Interleukin-6, decreased adiponectin levels, hyperuricaemia, elevated White Blood Cell (WBC) count, endothelial dysfunction, polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD) and others].[2,3,7,9] Furthermore even though an individual may or may not be identified as having the MS, it is strongly recommended that signs and symptoms associated with the MS should be treated individually and aggressively as each one will confer a degree of risk to the development of chronic disease and specifically CVD.[8]

Table I: Criteria for clinical diagnosis of the metabolic syndrome[2]

Measure Categorical Cut Points *The presence of 3 of 5 risk factors constitutes a diagnosis of the metabolic syndrome*	
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≤ 1.7 mmol/L
Reduced HDL-C (drug treatment for	≤ 1.0 mmol/L in males
reduced HDL-C is an alternate indicator†)	≤ 1.3 mmol/L in females
Elevated blood pressure (antihypertensive drug treatment in apatient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≤ 5,6 mmol/L

HDL-C indicates high-density lipoprotein cholesterol.
* It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.
† The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose Ω-3 fatty acids presumes high triglycerides.
‡ Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

Apart from identification of an increased risk specifically for the development of CVD or diabetes, and using the identification of the MS as a indication for early medical intervention and prevention strategies, perhaps the most valuable lessons that are taught to us by the MS is confirmation that certainly obesity, poor dietary practices and reduced activity levels interacting with genetic and metabolic factors almost guarantee a complex metabolic derangement that in turn is associated with disease.[10,11]

Can we connect the dots?

One of the primary reasons for identifying a disease process, as in this case the MS, would be to understand its cause and provide guidelines for prevention, if possible, appropriate treatment intervention and resolution of the disease state.[7,8,10] Unfortunately, the exact cause of the MS still appears to be elusive and as a result some controversy still exists about whether the MS is a true syndrome or a mixture of unrelated phenotypes.[2] A number of suggestions regarding the clustering of abnormalities and their precipitating cause(s) have been discussed and explored in the medical literature, and certainly there is no definitive answer at this time. Insulin resistance has, however, been identified as an underlying factor[7] and variability in insulin sensitivity has been largely attributed to differences in adiposity (25%), fitness (25%) and genetics (50%).[8] However, a hypothesis that seems to hold some further value, is the concept of oxidative stress as a pathogenic mechanism underlying insulin resistance, diabetes and cardiovascular disease.[12]

Poor diet quality and a hypercaloric diet-link with oxidative stress and insulin resistance

Muscle and adipose tissue are primarily involved with the development of insulin resistance. When energy intake exceeds energy expenditure, there is a substrate-induced increase in the citric acid cycle, which in turn generates an excess of mitochondrial NADH (mNADH) and consequent reactive oxygen species (ROS). It has been proposed that muscle and adipose tissue cells protect themselves against harmful effects of ROS, by reducing the formation of ROS and/or enhancing the removal of ROS. Preventing a build-up of mNADH is achieved by inhibiting insulin-mediated glucose disposal and inhibiting the entrance of substrates (pyruvate, fatty acids) into the mitochondria, this in turn helps to attenuate the formation of ROS. It has been proposed that excessive NADH generation can be prevented through the inhibition of free fatty acid (FFA) oxidation. An increase in intracellular FFA in the cell cytoplasm, in turn, leads to reduced levels of insulin sensitive glucose transporter GLUT4 (C-GLUT4) translocation to the cell membrane, resulting in resistance to insulin mediated glucose disposal in muscle and adipose tissue. According to this hypothesis, IR can be considered a compensatory mechanism that develops to protect cells against further glucose and fatty acid uptake and therefore oxidative damage.[12]

Many studies support this hypothesis in that antioxidants have been shown to improve insulin sensitivity. Several clinical trials have demonstrated that treatment with vitamin E, vitamin C, or glutathione improves insulin sensitivity in insulin-resistant individuals. The recent finding that insulin resistance is associated with reduced intracellular antioxidant defence status in humans also support this hypothesis.[12]

The link with β-cell dysfunction and endothelial dysfunction – key features of the MS

It is rational to suggest that what occurs in muscle and fat cells may also take place in other cells, specifically in α-cells and endothelial

cells. What is more, these types of cells may be even more severely affected by a hypercaloric diet. α-cells and endothelial cells are not dependent on insulin for glucose disposal, which is achieved via facilitative diffusion.[12] When such cells are exposed to elevated levels of glucose or fatty acids, they are not able to down regulate the influx of nutrients through insulin resistance, and have to permit intracellular concentrations of these nutrients to increase. Ongoing exposure to high glucose and/or elevated FFA levels, or a combination of both, has been suggested by a number of research papers to be responsible for α-cell dysfunction and apoptosis.[12] It is also important to note that these cells are highly vulnerable to ROS, as antioxidant enzymes are in short supply in these cells. It has been shown that oxidative stress has the ability to damage mitochondria and in turn result in a markedly blunted insulin secretion by α-cells.[12]

It is well known that IR is associated with endothelial dysfunction, and there is evidence that indicates that oxidative stress is associated with endothelial dysfunction, which in turn contributes to CVD. Glucose and FFA overload can be expected to influence endothelial cells as they do α-cells via oxidative stress, and a number of studies confirmed such a relationship.[12] There is also convincing evidence that FFA may produce the same consequences and increase oxidative stress and induce endothelial dysfunction, which can be reversed by antioxidants.[12]

Oxidative stress, Inflammation and Insulin resistance

The idea that oxidative stress is the common denominator underlying insulin resistance, CVD and type 2 diabetes, may explain the occurrence of inflammation in all these conditions. It is also well known that inflammation is one of the consequences of oxidative stress, and the mechanism that generates the mediators of inflammation include adhesion molecules and interleukins.[12] It is also worthwhile recognising that the subclinical pro-inflammatory state observed in many conditions including atherosclerosis, ageing and cancer, may well be associated with an over-production of free radicals by the mitichondria. This theory is supported by in vivo studies, showing that glucose and FFA cause inflammation through oxidative stress, and they have a cumulative and independent effect, and that antioxidants can, at least partially, ameliorate/reverse the occurrence.[12]

The way forward

The abnormalities associated with the MS can be viewed in clusters or independently. What is known currently is that these abnormalities are indicative of a metabolic derangement associated with increased disease risk specifically for cardiovascular disease and diabetes. We do not know categorically at present what the exact causes of the syndrome's many abnormalities are, or, for that matter, why most abnormalities do not occur collectively in all individuals. What is clear though is that obesity, inactivity and diet quality play a pivotal role in preventing and treating the MS and/or its associated abnormalities and, by inference at this stage, chronic disease. Genetic predisposition is clearly an uncontrollable risk factor, but those predisposed to diabetes and CVD would be in need of more intensive intervention(s) and would need stricter adherence to the recommended dietary and lifestyle practices to prevent or treat abnormalities associated with the MS and end-stage disease. It appears therefore that practitioners should continue to advise patients on what they always have done regarding diet and lifestyle change, with some necessary adjustments toward improved diet quality and improved micronutrient intake, which current evidence suggests may well play a key role in preventing oxidative stress, inflammation and IR.

Weight loss has been known to improve features of the MS and it has also been shown to reduce oxidative stress and to improve each component of the MS.[3,10] Practitioners should promote a low glycaemic load (GL) diet, as high GL diets have been linked with cardiovascular events and glucose spikes with endothelial dysfunction.[10,14,16]

Inflammation is an integral part of the MS that is worsened by the pro-inflammatory profile of the western diet. The available evidence is mostly supportive of benefits to be derived from diets rich in omega-3 fatty acids and other unsaturated fats, natural antioxidants in fruit and vegetables, and fibre in nuts and whole grains by patients with the MS.[10,15]

Supplementation with omega-3 fatty acids is an emerging treatment modality and should be strongly considered in patients unable to consume the required two fatty fish meals per week[10,13]. Additionally, one should encourage regular exercise – "a little is good and more is better" [10] ,and finally, referral to a dietitian should be considered for long-term reinforcement and follow up.[10]

Conclusion

The value of identifying the MS would appear to be a prudent approach for "quantifying" individual risk for CVD and diabetes and the presence of symptoms and signs of the syndrome should be accompanied by a search for other comorbidities. Risk factors for CVD, whether identified in clusters or separately should be treated appropriately, regardless of a diagnosis of the MS. Diet and lifestyle changes remain the cornerstone of treatment for the MS and associated abnormalities whether they present in clusters or individually. Greater emphasis needs to be placed on diet quality and intake of micro-nutrients, and, more specifically, nutrients with antioxidant properties.

References

1. Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. Annu Rev Med 1993;44:121–31. (Abstract)
2. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT. Harmonizing the metabolic syndrome: a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity. Circulation;120:1640–1645.
3. Einhorn D. ACE Position Statement. Endocrine Practice 2003;9(3):240–252.
4. Liao Y, Kwon S, Shaughnessy S, Wallace P, Hutto A, Jenkins AJ, Klein RL, Garvey WT. Critical evaluation of adult treatment panel III criteria in identifying insulin resistance with dyslipidemia. Diabetes Care 2004;27(4):978–983.
5. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. Lancet 2005;366:1059–1062.
6. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752.
7. Kahn R. Is the metabolic syndrome a real syndrome? Metabolic syndrome: Is it a syndrome? Does it matter? Circulation 2007;115:1806–1811.
8. Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 2006;83;1237–47.
9. Rizvi AA. Cytokine biomarkers, endothelial inflammation and atherosclerosis in the metabolic syndrome: emerging concepts. Am J Med Sci 2009;334:310–318.
10. Blaha MJ, Bansal S, Rouf R. A practical ABCDE approach to the metabolic syndrome. Mayo Clin Proc 2008;83:932–941.
11. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? Nutr Metab Cardiovascular Dis 2004;14:228–232.
12. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arterioscler Thromb Vasc Biol 2004;24:816–823.
13. Lichtenstein AH, Appel LJ, Brands M, Daniels MCS, Franch HA, Franklin B, Kris–Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: A Scientific Statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82–96.
14. Schleicher E, Friess U. Oxidative stress, AGE, and atherosclerosis. Kidney International 2007;72:S17–S26.
15. Bengmark S. Impact of nutrition on ageing and disease. Current Opinion in Clinical Nutrition and Metabolic Care 2006;9:2–7.
16. Bullo M, Casas-Agustench P, Amig-Correig P, Aranceta J, Salas-Salvado J. Inflammation, obesity and co-morbidities:the role of diet. Public Health Nutrition 2007:10(10A):1164–1172.

Glucose: the worst of all evils?

Prins A, (RD/SA)
Little Company of Mary Medical Centre, Groenkloof, Pretoria, South Africa
Correspondence to: Me Arina Prins, e-mail: arina.p@internists.co.za

Abstract

The acute phase response is associated with metabolic derangements, including hyperglycaemia. Hyperglycaemia is associated with adverse clinical outcomes, including increased morbidity and mortality in various patient populations. The obvious question is: does tight blood glucose control improve morbidity and mortality in critically ill patients? Tight glycaemic control (TGC) or intensive insulin therapy (IIT) has become a major area of research, debate and controversies. The belief that hyperglycaemia is a physiological response and intervention is only warranted when the renal threshold is exceeded rapidly changed to aggressive control and, currently, clinical practice is moving to a mid-point between the two.

S Afr J Clin Nutr 2010;23(1) Supplement:S50-S54

Introduction

Hyperglycaemia is common in critically ill patients.[1,2,3,4,5] The acute phase response is associated with the abundant production of pro- and anti-inflammatory mediators and counterregulatory hormones, causing pathologic metabolic derangements.[6,7] Hyperglycaemia occurs secondary to elevated levels of cortisol, epinephrine, norepinephrine, glucagon resulting in gluconeogenesis and glycogenolysis, as well as insulin resistance.[5,6]

Hyperglycaemia may cause harm through a direct toxic effect, increased intracellular oxidative stress due to higher mitochondrial peroxide production,[5] altered cytokine production and impaired phagocytosis.[6] Hyperglycaemia is a marker of severity of illness, and is associated with adverse outcomes, including increased morbidity and mortality in various patient populations.[2,3,5,6,8,9] The adverse consequences include increased infectious complications and higher mortality in trauma patients,[10,11,12] worse neurological outcome in a subset of traumatic brain injury (TBI) patients,[13] poor functional recovery and higher mortality in stroke patients,[14,15,16,17] and an increased morbidity and mortality after myocardial infarction[18,19] as well as higher morbidity and mortality in other critically ill patients.[20,21] In addition, hyperglycaemia during critical illness is associated with worse long-term outcomes such as degree of disability after a stroke[14] and risk for mortality and congestive heart failure one year after a myocardial infarction.[23]

The obvious question thus is: will intensive insulin therapy (IIT) improve morbidity and mortality in critically ill patients?

The past

When the first randomised clinical trials on blood glucose control in critically ill patients were first reported in 1995,[23] physicians did not place a high priority on blood glucose (BG) control.[23] Hyperglycaemia was considered part of the usual clinical course of critical illness and often not treated until levels exceeded the renal threshold of 12 mmol/L when it induced glucosuria and hypovolaemia.[24] Insulin was administered according to a sliding scale and few protocols tried to match insulin dose to nutritional intake and the effectiveness of these protocols were not assessed.[23]

Tight glucose control

One of the first randomised clinical trials on Tight Glucose Control (TGC), utilising intravenous insulin followed by multiple dose insulin therapy, was the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study. Mortality at one year was reduced by 26%.[22] It is, however, unclear whether this outcome was due to tight control during hospitalisation or due to better diabetes management after discharge.[1] The multicentre DIGAMI 2 trial could not reproduce these results and found no effect on morbidity or mortality after two years of follow up, possibly due to an inability to recruit an adequate number of patients[25,1] and the inability to achieve strict control.[26]

The landmark study by Van Den Berghe, et al (Leuven 1) was the first large randomised trial in critically ill patients in a surgical intensive care unit (SICU) (mainly coronary bypass surgery, 13% with diabetes) with hyperglycaemia and included both diabetic and non-diabetic patients.[27] Aggressive control, (BG 4.5–6.0 mmol/L) was associated with a significant reduction in ventilator support and

renal replacement therapy with a significant cost saving. The ICU mortality rate was reduced from 8% in the control group to 4.6% in the TGC group, and similarly, in-hospital mortality was reduced from 10.9% to 7.2%. The relative risk of in-hospital death was thus reduced by 33.9%. The benefit occurred in patients who remained in the ICU for > 5 days. The number of deaths in the first five days was similar in both groups.[27]

The results were very different when the same authors proceeded to apply the same protocol to medical ICU patients (MICU) (Leuven 2).[28] The mortality rate was lower in patients who stayed in ICU for ≥ 3 days, but higher in those that stayed < 3 days. The mortality reduction in the group who stayed longer in ICU was much smaller (6%) than the 42% reduction seen in the surgical ICU study.[28] From these two studies it seems that the beneficial effect was more pronounced in severely ill patients requiring prolonged ICU care.[5]

These studies led to the publication of guidelines for the management of severe sepsis and shock which recommended TGC as an important part of management[29] and was again included in the updated version of the guidelines in 2008.[30] It is surprising that TGC was widely adopted after the Leuven 1 study, since the authors stated that their patients were: 1) ventilated surgical patients, 2) admitted to ICU after predominantly cardiac surgery and 3) that the results can not be extrapolated to other groups of ICU patients. The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial applied the same protocol to septic patients and achieved lower BG concentrations, but no decrease in mortality.[31] Two studies did not find a decrease in mortality with TGC in mixed ICU populations.[3,32]

A large multi-centre trial, the NICE-SUGAR trial, compared patients whose blood glucose concentrations were maintained below 6.7 mmol/L (TGC) with those whose blood glucose was kept between 7.8–10.0 mmol/L in MICU and SICU patients in 42 hospitals. Although lower BG concentrations were achieved, TGC did not improve outcomes in terms of length of stay (LOS) in ICU or hospital, median number of days on mechanical ventilation or renal replacement therapy. Hypoglycaemia was recorded in 6.8% of the TGC group and 0.5% in the control group. Mortality was significantly higher in patients with tight control (27.5%–24.9%).[2]

Two recent meta-analyses have also evaluated TCG. The first one (done prior to the NICE-SUGAR study) found a significant decreased incidence in sepsis (subgroup analysis suggests that it was limited to SICU patients), no association with new need for dialysis, an increased risk for hypoglycaemia and no impact on mortality.[33] The second meta-analysis included the results from the NICE-SUGAR study confirmed these findings with regards to hypoglycaermia, but suggested that there is a mortality benefit with TGC surgical ICU patients.[9]

Methodological differences

The different outcomes between the Leuven 1[27] and the VISEP[31] trials were probably due to differences in design and study population. The VISEP trial was designed as a four arm study comparing two resuscitation fluids (10% pentastarch versus modified Ringer's lactate) as well as the efficacy and safety of TGC which may have had some influence on the outcomes. Furthermore, this study included patients with severe sepsis, known to be at a higher risk for hypoglycaemia,[1] while the Leuven 1 included mainly coronary bypass surgery patients. In addition, the fluid resuscitation arm of the study was also suspended due to an increased risk of organ failure (10%) in the pentastarch arm. This reiterates the point that the resuscitation fluid rather than the glucose control may have caused the higher mortality.

The VISEP trial, as well as the Glucontrol study,[34] was stopped due to high rates of hypoglycaemia (12.1/18.6% respectively), but there was no difference in mortality. An additional factor for the cessation of the Glucontrol study was a high rate of unintentional protocol violations.[35] It is also possible that the low number of patients per centre may have contributed to the lack of treatment effect.[5] The Glucontrol study was only released in abstract form, thus it is not possible to assess methodology fully.

The different outcomes in terms of mortality between the Leuven studies[27,28] and the two mixed ICU population studies[3,32] may possibly be explained by the different study designs, populations and the age difference in the study populations.[3,32] Another aspect that may indicate some difference in the study population is the high in-hospital mortality (10.9%) in the control group of the Leuven 1 study.[27] A subsequent study to investigate this point found an in-hospital mortality rate in similar patients in Australia to be only 3.8%, much lower than the mortality of both the treatment and control groups in the Leuven 1 trial.[36]

The NICE-SUGAR study and the Leuven 1 and 2 studies are most often compared in an effort to come to a conclusion with regards to TGC. However, various differences between these studies need to be pointed out. The Leuven studies were single centre trials while the NICE-SUGAR study was a multicentre trial. The accuracy of measuring tools at different centres and the experience of the nursing staff with TGC come into play.[1,24] Avoiding variable blood glucose and exact titration requires experience of the nursing staff[1,24] which may have been lacking in a multicentre trial.

It was also noted that the control group in the NICE-SUGAR study had an average BG of 7.8–10,0 mmol/L while it was 10.0–11.1 mmol/L in the Leuven studies.[2,27,28,37] This essentially means that the control group was already better controlled by targeting an intermediate blood glucose level, which makes a direct comparison between the studies difficult. It was speculated that the better control in the control group might have improved outcomes to such a degree that tighter control would not have resulted in a more significant benefit.[9,24,37] Van Den Berghe, et al (2009) agreed with this conclusion and suggested that an intermediate target range may be preferable in critically ill patients.[24]

In addition, the NICE-SUGAR (MICU and SICU) study is often compared to the Leuven 1 study, which was on SICU patients (predominantly cardiac surgery) only. In this regard, the NICE-SUGAR study results are more similar to that of the two mixed ICU studies.[3,32]

Furthermore, various other differences between the studies may have affected outcomes, such as early nutrition support and its mode of administration as well as energy content, and BMI status.[24,37] It is also important to note that some studies already described included both diabetic and stress induced hyperglycaemia patients, which is unfortunate, since recent data indicates that the two settings are different.[38] A comparison of outcomes in patients with known diabetes to those without diabetes after implementation of a moderate glycaemic control protocol (6.9 mmol/L) showed a significant reduction in mortality in non-diabetic patients, but not in those with known diabetes.[39] It is also unfortunate that the diabetic sub-sets were presented differently in the Leuven and NICE-SUGAR studies (type 1 and 2 versus on insulin or on oral medication/diet) making comparisons and conclusions even more difficult.

Other differences between the Van Den Berghe studies and subsequent studies, which are not comprehensively described herein, include: different target ranges for blood glucose control, differences in the definition of hypoglycaemia, duration of hyperglycaemia preceding the intervention and varying levels of expertise with the therapy among the ICU nurses and a high nurse to patient ratio in the Leuven studies,[1,9,24,38] APACHE scores, age of patients, the degree with which blood glucose levels fluctuated in an individual patient as well as quality of the glucose control process itself, the case mix, associated therapy (e.g. corticosteroids), the existing variability in the intervention evaluation, the timing of the initiation of IIT and the variability in outcomes measures.[4,9,35,36,40]

Mechanisms of potential beneficial effects of tight control

Irrespective of the limitations in comparing the described studies, the question still remains whether insulin therapy *per se* improved mortality directly through modulating the inflammatory response or indirectly through improving hyperglycaemia, and consequently metabolism (Table I). In this regard, insulin is an anabolic and anti-catabolic hormone. Insulin is also a regulator of the inflammatory and immune responses, which may contribute to the reduced mortality after IIT in some studies.[41] Furthermore, sub-maximal doses of insulin have been shown to enhance skeletal muscle protein anabolism in severely burned (> 60% TBSA) patients,[42] which may also contribute to reduced mortality in certain patients groups.

Hypoglycaemia

The major obstacle with TGC appears to be hypoglycaemia, which is possibly the major contributing factor to the poor outcomes documented in some studies. It thus appears that in order to benefit from TGC, hypoglycaemia needs to be avoided. The mechanism by which hypoglycaemia increases mortality in severe sepsis and shock has not been fully investigated. One possible mechanism is brain damage because of an energy deficit in the brain through hypglycaemia.[6] Many recent studies have reported significant rates of hypoglycaemia with TGC (defined as BG < 2.2 mmo/L). The incidence of hypoglycaemia in tight control groups varied from 7–20% and was as low as 0.5% in control groups in ICU-based studies (Table II).[23]

Table I: Possible mechanisms of beneficial effects of insulin

Wade 2008[43]	Hyperglycaemia alters cytokine production and phagocytosis
Vanhorebeek et al, 2005[44]	Strict blood glucose control protects hepatocyte mitochondrial ultrastructure and function
Herman et al, 2007[45] Herman et al, 2009[46]	Intensive insulin therapy prevents critical polyneuropathy/myopathy
Dugo et al, 2006[47]	Insulin inhibits glycogen synthase kinase-3β, contributes to protective effect of insulin against organ injury/dysfunction caused by excessive systemic inflammation, independent from its effect on glucose
Bopp et al, 2008[48]	Tight glycaemic control may decrease AGE (advanced glycation end product) formation and thereby reduce the inflammatory response mediated through AGE and RAGE (receptor of advanced glycation end product) interaction
Jeschke et al, 2002[49] Jeschke et al, 2004[50]	Insulin decreases pro-inflammatory cytokines and proteins and increases the anti-inflammatory cascade in burned rats and children (BG between 6.6–10 mmol/IL).

Table II: Incidence of hypoglycaemia with TGC

STUDY	TGC	CONTROL
Leuven 1[27]	5.1%	0.8%
Leuven 2[28]	18.7	3.1%
Glucontrol[34]	9.8% (moderate) 41.1% (mild) 8.6%	2.7% (moderate) 9.6% (mild) 2.4%
NICE-SUGAR[2]	6.8%	0.5%
VISEP[31]	12.1%	2.1%
De La Rosa et al[32]	8.5%	1.7%

Juneja et al (2009) found that the most common contributing cause for hypoglycaemia was measurement delay.[8] It is known that severe hypoglycaemia increases stress hormone levels in normal individuals, but adequacy of this response in critically ill patients with already increased stress hormone levels is not known.[23] Furthermore, the majority of hypoglycaemic episodes has been shown to occur during unplanned interruption of feeding.[51,52] From the Leuven studies it also appears that medical patients might be at a higher risk for hypoglycaemia, possibly due to higher necessity for treatments known to affect blood glucose control such as inotrope support, corticosteroid administration and renal replacement therapy. Liver failure and kidney failure, which increase the vulnerability to hypoglycaemia, may also partly explain this observation.

Another reason for the higher mortality with TGC may be due to the limitations in measuring glucose using the point-of-care devices (glucometers), since the glucose concentration obtained by these devices differs significantly from those obtained by conventional

laboratory methods.[53] In the NICE-SUGAR study only 60.1% of the hypoglycaemic episodes were confirmed by laboratory measurement.[2] A variety of glucometers were allowed in the NICE-SUGAR study. The accuracy of some types of glucometers has been shown to be poor in the ICU setting.[54] In addition, many critically ill patients are anaemic and it has been shown that a haematocrit of < 34% produces systematic errors in glucometer measurements.[55] Moreover, anaemia results in falsely elevated BG levels, while polycythaemia results in low values.[56] It is interesting in this regard that a correction formula has been developed which, when applied to device derived glucose concentrations, was associated with a 78% decrease in hypoglycaemia in the presence of TGC practices.[55]

Hirasawa et al (2009) used a novel approach to indicate "good" and "bad" responders to tight glycaemic control.[6] An interleukin-6 (IL-6) level of 1000 pg/ml can be used to diagnose systemic inflammatory response syndrome (SIRS) or hypercytokinaemia. Applying TGC (6.6–8.3 mmol/L) to patients with severe sepsis and septic shock resulted in a success rate of TGC was only 53%. When the researchers divided the patients into subgroups according to IL-6 levels on admission to ICU, they found that the success rate of TGC was relatively high in those with an IL-6 < 1000 mg/dl on admission, but very low in those with a level of > 10000 pg/ml.[6]

A protocol prescribing the control process may improve BG control.[4] TGC (4.4–4.6 mmol/L) in ICU patients, by using a computerised insulin dosing algorithm, resulted in hypoglycaemia in only 4.25% patients with 97.5% achieving target range and remained on target 73.4% of the time.[8] Unfortunately this study was not randomised, it was retrospective in nature and employed various BG sampling methods. The SPRINT protocol was applied in a general ICU to achieve TGC (4.4–6.1mmol/L). The implementation of the SPRINT protocol resulted in only 9.0% of all measurements being below 4.4 mmol/L, 3.8% below 4 mmol/L and 0.1% of measurements below 2.2 mmol/L. Hospital mortality was reduced for ≥ 3 (from 34.1% to 25.4%), ≥ 4 (from 34.3% to 23.5%) and ≥ 5 days (from 31.9% to 20.6%).[7]

Recommendations

Some recent recommendations for BG control targets (Table III) and safe recommendations for implementation of TGC (Table IV) are presented in the respective Tables.

Conclusion

Hyperglycaemia is associated with adverse effects in the critically ill patient. Studies investigating the effect of TGC, unfortunately, to date have not provided a definitive answer to the question whether TGC will improve mortality. The greatest risk in some studies on TGC has been shown to be hypoglycaemia. Future research needs to focus on blood glucose target for different populations and the design of effective tools to reach the targets safely. Furthermore, a distinction should be made between diabetic patients and other ICU patients, and the effect of nutrition support protocols and glucose variability should be assessed. In the meantime, it would be prudent to practice a moderate control target in the ICU, in general, with particular attention to settings that contribute to the precipitation of hypoglycaemia.

Table III: Recommemdations for BG targets in critically ill patients

STUDY	RECOMMENDATION
NICE-SUGAR[2]	< 10 mmol/L
Merz and Finfer, 2008[5]	Each ICU should define a blood glucose range which can be achieved without causing a significant increase in severe hypoglycaemia, and which fits within the constraints of their nursing and economic resources. Upper limit: 7.7–9.9 mmol/L
Reider et al, 2009[1]	7.7–9.9 mmol/L for the majority of critically ill patients; 6.05–7.7 mmol/L for surgical ICU patients
Preiser et al, 2007[35]	7.7–9.9 mmol/L
Americam Dietetic Aassociation[57]	7.7–9.9 mmol/L
ASPEN[58]	6.05–8.25 mmol/L

Table IV: Minimal safe requirements

- Close monitoring
- Frequent checks of blood glucose levels
- Systematic use of intravenous insulin infusion
- Validated protocols
- Training of staff
- Close collaboration between nursing and medical staff
- Appropriate and standardised means to measure blood glucose (preferably laboratory testing)
- Only arterial or venous samples
- Attention to nutrition support protocols
- Attention to feeding interruptions

References

1. Reider J, Donihi A, Korytkowski MT. Practical implications of the revised guidelines for inpatient glycemic control. Polskie Archiwum Medycyny Wewnętrznej. 2009;119(12):801–8.
2. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
3. Treggiari MM, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. Critical Care. 2008;12:R29.
4. Eslami S, De Keizer NF, De Jonge E, Schultz MJ, Abu-Hanna A. A systematic review on quality indicators for tight glycaemic control in critically ill patients: need for an unambiguous indicator reference subset. Critical Care. 2008;12:R139.
5. Merz TM, Finfer S. Pro/con debate: Is intensive insulin therapy targeting tight blood glucose control of benefit in critically ill patients? Critical Care 2008; 12:(2)212.
6. Hirasawa H, Oda S, Nakamura M. Blood glucose control in patients with severe sepsis and septic shock. World J Gastroenterol 2009;15(33):4132–6.
7. Chase G, Shaw G, Le Compte A, et al. Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. Critical Care. 2008;12:R49.
8. Juneja R, Roudebush CP, Nasraway, SA, Golas, AA, Jacobi J, Carroll J,Nelson D, Abad VJ, Flanders SJ. Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time. Critical Care. 2009;13:R163.
9. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009;180(8):821–7.
10. Yendamuri S, Fulda GJ, Tinkoff GH: Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003;55:33–8.
11. Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM: Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma. 2005;59:80–3.
12. Gale SC, Sicoutris C, Reilly PM, Schwab CW, Gracias VH: Poor glycemic control is associated with increased mortality in critically ill trauma patients. Am Surg. 2007; 73:454–60.

13. Rovlias A, Kotsou S: The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery. 2000;46:335–42.
14. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke. 2001;32:2426–32.
15. Badjatia N, Topcuoglu MA, Buonanno FS, Smith EE, Nogueira RG, Rordorf GA, Carter BS, Ogilvy CS, Singhal AB: Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. Crit Care Med. 2005; 33:1603–9.
16. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE, NINDS rt-PA Stroke Study Group: Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. Neurology 2002;59:669–74.
17. Gentile NT, Seftcheck M, Martin R: Blood glucose control after acute stroke: a retrospective study. Acad Emerg Med. 2003;10:432.
18. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet. 2000;355:773–8.
19. Malmberg K, Norhammar A, Wedel H, Rydén L: Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation. 1999;99:2626–32.
20. Freire AX, Bridges L, Umpierrez GE, Kuhl D, Kitabchi AE: Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. Chest. 2005;128:3109–16.
21. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann MC, Perencevich EN: Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med. 2005;33:2772–7.
22. Malmberg K, Ryde´n L, Efendic S, Herlitz J, Nicol P, Waldenstro¨m A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol. 1995;26:57–65.
23. Comi J. Glucose Control in the Intensive Care Unit: A Roller Coaster Ride or a Swinging Pendulum? Ann Intern Med. 2009;150:809–11.
24. Van den Berghe G, Schetz M, Vlasselaers D, Hermans G, Wilmer A, Bouillon R, Mesotten D. Clinical review: Intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab. 2009;94(9):3163–70.
25. Malmberg K, Ryden L, Wedel H, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. Eur Heart J. 2005;26:650–61,
26. Collier B, Dossett LA, May AK, Diaz JJ. Glucose Control and the Inflammatory Response. Nutr Clin Pract. 2008;23(1):3–15.
27. Van Den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx, F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001;345(19):1359–67.
28. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354(5):449–61.
29. Dellinger RP, Carlet J, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2004;30(4):536–55.
30. Dellinger RP, Levy M, Carlet J, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34(1):17–60.
31. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K, German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008; 358(2):125–39.
32. De La Rosa G, Donado JH, Restrepo AH, et al. Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Critical Care. 2008;12:R120.
33. Wiener RS; Wiener DC; Larson RJ. Benefits and Risks of Tight Glucose Control in Critically Ill Adults: A Meta-analysis. JAMA. 2008;300(8):933–44.
34. Devos P, Preiser J, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the glucontrol study [European Society of Intensive Care Medicine 20th Annual Congress abstract 0735]. Intensive Care Med. 2007;33(suppl 2):S189.
35. Preiser JC, Devos P. Clinical experience with tight glucose control by intensive insulin therapy. Crit Care Med. 2007;35(9) Suppl):S503–7.
36. Egi M, Bellomo R, Stachowski E, French CJ, Hart G, Stow P, Li W, Bates S: Intensive insulin therapy in postoperative intensive care unit patients: a decision analysis. Am J Respir Crit Care Med. 2006;173:407–13.
37. Inzucchi SE, Siegel MD. Glucose control in the ICU—how tight is too tight? [Editorial]. N Engl J Med. 2009;360:1346–9.
38. Fahy BG, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. Crit Care Med. 2009;37(5):1769–76.
39. Krinsley JS, Jones RL: Cost analysis of intensive glycemic control in critically ill adult patients. Chest. 2006;129:644–50.
40. Honiden H, Schultz A, Im SA, Nierman DM, Gong MN. Early versus late insulin administration in critically ill patients. Intensive Care Med. 2008;34(5):881–7.
41. Deng H, Chai. The effects and mechanisms of insulin on systemic inflammatory response and immune cells in severe trauma, burn injury, and sepsis. International Immunopharmacology. 2009;9:1251–9.
42. Ferrando AA, Chinkes DL, Wolf SE, Matin S, Herndon DN, Wolfe RR. A Submaximal Dose of Insulin Promotes Net Skeletal Muscle Protein Synthesis in Patients With Severe Burns. Annals of Surgery. 229(1):11–18.
43. Wade CE. Hyperglycemia may alter cytokine production and phagocytosis by means other than hyperosmotic stress. Crit Care. 2008;12:182.
44. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet. 2005;365:53–9.
45. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, Bruyninckx F, Van den Berghe G. Impact of intensive insulin therapy on neuromuscular omplications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 2007;175:480–9.
46. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev 2009.
47. Dugo L, Collin M, Allen DA, Murch O, Foster SJ, Yaqoob MM, Thiemermann C. Insulin reduces the multiple organ injury and dysfunction caused by coadministration of lipopolysaccharide and peptidoglycan independently of blood glucose: role of glycogen synthase kinase-3beta inhibition. Crit Care Med. 2006;34:1489–96.
48. Bopp C, Bierhaus A, Hofer S, Bouchon A, Nawroth PP, Martin E, Weigand MA. Bench-to-bedside review: The inflammation-perpetuating pattern-recognition receptor RAGE as a therapeutic target in sepsis. Crit Care. 2008;12:201.
49. Jeschke MG, Einspanier R, Klein D, Jauch K-W. Insulin Attenuates the Systemic Inflammatory Response to Thermal Trauma. Molecular Medicine. 2002;8(8):443–50.
50. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. Ann Surg. 2004. 239:553–60.
51. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med. 2003. 31:359–366.
52. Clayton SB, Mazur JE, Condren S, et al. Evaluation of an intensive insulin protocol for septic patients in a medical intensive care unit. Crit Care Med. 2006. 34:2974–2978.
53. Shearer A, Boehmer M, Closs M, Dela Rosa R, Hamilton J, Horton K, McGrath R, Schulman C. Comparison of glucose point-of-care values with laboratory values in critically ill patients. Am J Crit Care. 2009. 18(3):224–30.
54. Vlasselaers D, Van Herpe T, Milants I, Eerdekens M, Wouters PJ, De Moor B, Van den Berghe G 2008 Blood Glucose Measurements in Arterial Blood of Intensive Care Unit Patients Submitted to Tight Glycemic Control: Agreement between Bedside Tests. J Diabetes Sci Technol. 2:932–938.
55. Pidcoke HF, Wade CE, Mann EA, Salinas J, Cohee BM, Holcomb JB, Wolf SE. Anemia causes hypoglycemia in intensive care unit patients due to error in single-channel glucometers: Methods of reducing patient risk. Crit Care Med. 2009. Sep 28.
56. Scott MG, Bruns DE, Boyd JC, Sacks DB. Tight glucose control in the intensive care unit: are glucose meters up to the task? Clin Chem. 2009;55:;18–20.
57. ADA. Standards of medical care in diabetes – 2010. 2010. Diabetes Care. 22(suupl 1):S11–S61.
58. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. Crit Care Med. 2009.37(5).

The use of specialised enteral formulae for patients with diabetes mellitus

Blaauw R
Division of Human Nutrition, Stellenbosch University, Stellenbosch, South Africa
Correspondence to: Prof R Blaauw, e-mail: rb@sun.ac.za

Abstract

The majority of enteral nutrition products for diabetes mellitus have a carbohydrate content of 30–45% and fat between 40–49%, mainly monounsaturated fat, with a mix of soluble and insoluble fibre (total of 14–24 g/l). Does this have short- and long-term benefits and which component(s) is/are crucial for the outcome or is it the combination that counts? Both manipulations of DM specific enteral formulae, i.e. addition of fibre and altered carbohydrate to fat percentage seem to be effective for short-term glucose control, but do not show convincing evidence regarding lipid management. In terms of gastro-intestinal function, there seems to be adequate evidence that fibre plays an important role for the management of diarrhoea and constipation. The implications of high fat intake on the longer-term, especially in patients suffering from gastroparesis, are less clear.

S Afr J Clin Nutr 2010;23(1) Supplement:S55-S57

Introduction

The medical nutrition therapy of a patient with diabetes mellitus (DM) poses many challenges to the health care provider. In order to reach the goals of treatment, careful consideration of the different treatment options needs to be investigated.

The goals of nutritional therapy for DM include the maintenance of as near-normal blood glucose levels as possible, the achievement of optimal blood lipid levels, the prevention and treatment of acute and chronic complications of diabetes; while concurrently maintaining fluid balance in a patient receiving nutritional support.[1,2] Another important factor in the nutritional management of a diabetic patient is glycaemic control during enteral feeding since hyperglycaemia has been associated with an increased risk for infection in patients with DM and in ICU patients in general.[2,3] Current guidelines for blood glucose control in critically ill patients with and without DM, recommend keeping glucose values in the range of 6,1–8,3 mmol/L.[3,4] There is a higher incidence of severe hypoglycaemia in patients treated to tighter limits when blood glucose is maintained between 4.5 and 6.1 mmol/L.[4]

Diet composition

The ideal composition of the diabetic diet, specifically with regards to the carbohydrate and fat content, has received much attention and research in the last 15 years. From a high carbohydrate, low fat diet to a low carbohydrate, high fat diet, to a mixture of both. What has become more evident with time is that it is not only the total amounts, but rather the type of carbohydrate and fat that is important.[1]

The nutritional recommendations for individuals with DM of the American Diabetes Association for instance (Table I) indicate that in the 1990's, the recommended contribution to total energy (TE) of carbohydrate was 50–60%, fat had to be < 30% and no recommendations were made for glycaemic index (GI).[5] About 10–12 years later, the recommendations changed to the combination of carbohydrate and fat, especially monounsaturated fat (MUFA), contributing between 60–70% total energy, saturated fat < 7%, poly-unsaturated fat < 10%, trans fatty acids as low as possible and cholesterol < 300 ml per day. Still no GI recommendation was included.[6] From 2006 up to the present, no specific percentage recommendations are made for the percentage contribution of carbohydrate and fat in terms of total energy, but carbohydrate should be > 130 g per day, saturated fat < 7%, trans fatty acids as low as possible and cholesterol < 200 ml per day. Fibre intake should be 14 g/1000 kcal, with emphasis on low GI foods.[1,3]

The emphasis that was placed on increasing fat, especially MUFA, stemmed from research associating hypertriglyceridaemia with diets high in carbohydrate.[7] By decreasing the carbohydrate contribution and simultaneously increasing the fat contribution, especially MUFA, a positive outcome on lipid management, together with glucose control was found and this contributed to the changed recommendations. It was then thought that these high fat diets could result in weight gain, but studies proved that increased MUFA diets as part of an energy-controlled diet plan, would not result in weight gain.[2] The most recent guidelines take emphasis away from specific percentage contributions of carbohydrate and fat, and make room for a more individualised approach, but they do indicate minimum carbohydrate and maximum saturated fat intake. Also, current

Table I: Adaptations in the nutritional recommendations of the American Diabetes Association 1994–2006

Year	Carbohydrate	Fibre	Glycaemic index	Fat
1994[5]	50–60% TE	Consume a variety of foods	No recommendation	TF < 30% TE SF < 10% TE
2004[6]	CHO + MUFA = 60–70% TE	Similar to general public	No recommendation	SF < 7% TE TFA minimum PUFA < 10% TE Chol < 300 mg
2006[1]	CHO > 130 g per day	14 g/1000 kcal	Emphasis on low GI foods	SF < 7% TE TFA minimum Chol < 200 mg

TE = total energy; CHO = carbohydrate; GI = glycaemic index; TF = total fat; SF = saturated fat; MUFA = monounsaturated fat; PUFA = poly-unsaturated fat; Chol = cholesterol; TFA = trans fatty acids

recommendations define better the amount of fibre and place emphasis specifically on GI.

It is therefore to be noted that the composition of enteral formulae specific for the management of DM reflect the prevailing recommendations at the time a given formula became available. The majority of enteral nutrition products for DM have a carbohydrate content of 30–45% and fat between 40–49%, mainly monounsaturated fat, with a mix of soluble and insoluble fibre (total of 14–24 g/l). Does this composition of such products have short- and long-term benefits for the patient and which component is crucial for the outcome or is it the combination that really matters?

The role of fibre

Fibre is advantageous to the diabetic patient not only because it helps against constipation (insoluble fibre),[8,9] but also because it is known to decrease blood glucose and lipid levels (mainly soluble fibre).[8,9] This is achieved by the ability of fibre to regulate the absorption of glucose through reducing the rate of digestion and prolonging gastric emptying, thereby improving postprandrial blood glucose control.[10] The recommended fibre intake varies from 20–50 grams per day, or 14–25 g/1000 kcal (4200 kJ) and about 50% of fibre should be of the soluble type.[1,7,10] An adequate fluid intake is essential in patients receiving fibre-containing enteral nutrition, especially if long-term, to prevent constipation.[11]

Fibre supplementation of enteral nutrition is normally done in order to attempt to improve GIT tolerance i.e. improve diarrhoea; prevent constipation and improve glycaemic control.[8,12]

Elia et al[13] performed a systematic review and meta-analysis to determine the clinical significance of fibre-containing enteral formulae. They included 51 studies that met their inclusion criteria. The type of fibre used most in the studies was soy polysaccharides, followed by a fibre-mix of soluble and insoluble fibres or by other individual fibre components. In the hospitalised patients, fibre-containing feeds were well tolerated and resulted in improvements in clinical outcomes. The overall incidence of diarrhoea was significantly reduced by 32% (OR = 0,68, p = 0,03). The effect was most pronounced in those with a high incidence of diarrhoea at initiation of the formula. Due to heterogeneity between the studies, especially between the ICU studies, results should be interpreted according to ICU and non-ICU patient populations. In the ICU group, the incidence of diarrhoea was reduced by only 2% (OR = 0,98), but in the non-ICU group it was reduced by 58% (OR = 0,42, p = 0,001). This highlights the importance of group-specific analysis of data.

The amount of fibre consumed in the studies ranged from 14–34,9 g/day and did not show a significant relationship with the diarrhoea incidence.[13] The fibre intake did, however, show a significant positive relationship with faecal mass. The latter did not directly affect the prevalence of constipation, since even though the fibre-containing feeds resulted in less patients reporting constipation, the results were not significant. Bowel frequency was increased by fibre supplementation in patients with a low frequency at baseline and vice versa, with little effect on patients with a normal bowel frequency.[13]

When assessing outcomes of fibre-supplemented formulae versus an enhanced fibre intake in the diet, it should be remembered that modified fibres are being used in formulae in order to reduce the occurrence of blockage of feeding tubes. This might affect the metabolic pathways and water-holding properties of the fibre that could explain the differences in outcomes.[13] Also, assessing formulae using a single fibre source with those using fibre mixtures will also be expected to affect the outcome.

Carbohydrate and fat contribution to total energy

Some clinical studies have indicated that high carbohydrate (> 55%), low fat (< 30%) diets resulted in increased postprandrial plasma glucose and hypertriglyceridaemia as compared to lower carbohydrate (40–45%) and higher fat (45%), specifically monounsaturated fat (20–25%) diets.[1,7] The latter diet composition did not only result in better glucose control, but the lipid abnormalities were also improved. Other researchers found similar results, but additionally reported the total energy intake of the diet to be the deciding factor. In patients receiving reduced energy intake, high carbohydrate diets did not increase triglyceride levels. This was only found when a high energy intake was maintained. Because of the individual response to high carbohydrate diets, it is recommended that individual dietary adaptations should be made regarding the carbohydrate and fat composition in the diet of a given patient. Other researchers have reported that replacing saturated fats with polyunsaturated fat had similar results to replacing saturated fat with monounsaturated fats. Depending on the total energy and carbohydrate intake, as well as the individual response to the diet, saturated fat can therefore be replaced by either unsaturated fatty acid or carbohydrate.[1,2,7]

Studies comparing diabetes-specific formulae with standard formulae have reported a neutral effect on glucose control and lipid management[14]; a reduction in peak glucose values[15,16,17]; a reduced HbA1c profile[15,16]; lower postprandial glucose values[18]; reduced insulin requirements[16] and no significant effect on lipid values.[14,16,18]

Unfortunately, due to relatively small patient numbers and short duration of studies, as well as different feed compositions, it is difficult to compare results and to determine the clinical impact of the outcomes.

Elia et al[19] performed a systematic review and meta-analysis to determine the benefits of enteral nutrition support, specifically the use of diabetes-specific formulae for patients with DM. In total 23 studies were included of which 19 were RCT and the majority studied type 2 DM. Due to different study methodologies, relatively small numbers of studies were grouped together for subgroup analysis. Compared to standard formulae, DM specific formulae Studies comparing diabetes-specific formula with standard formula resulted in significantly lower postprandrial blood glucose rise (by 1,03 mmol/L), significantly smaller area under the curve (AUC) and insulin AUC values, and reductions in A1c by 0,6%. The effects on the blood lipid profile were less pronounced with no significant effects on cholesterol, LDL, HDL and triglyceride values. Also of importance was the finding that no significant differences in complication rates were reported. The authors concluded that DM specific formulae can result in improvements on blood glucose control.[19]

Conclusion

Do we really need specialised formulae for diabetes patients or can the patients be treated just as effectively with a standard polymeric formula with or without fibre? According to the ADA,[3] various studies have attempted to identify the ideal mix of macronutrients for patients with DM. It is unlikely that one such combination of macronutrients exists and therefore emphasis should be placed in individualised approaches.[1,3]

The majority of diabetes-specific enteral formulae on the market in South Africa contain a combination of different fibres, with an altered carbohydrate to fat ratio with emphasis on MUFA. The question can thus be asked which of these two main alterations i.e. addition of fibre or carbohydrate to fat manipulation is the most important and successful, or is it the combination of the two that is of the essence?

In all patients, fermentable fibres are effective for glucose control.[8,9] Since the dyslipidaemia of diabetes (type 2), especially hypertriglyceridaemia, is often disproportionate to the degree of hyperglycaemia, the latter needs to be monitored and treated individually.[2] Both manipulations of DM-specific enteral formula, i.e. addition of fibre and altered carbohydrate to fat percentage does not show convincing evidence regarding lipid management.[2,19]

In the critically ill patient in an ICU setting, the tolerance of fibre sources is dependent on the function of the gastro-intestinal tract and the use of fibre (quantity and type) should be reconsidered based on the given clinical setting. Patients at high risk of bowel dysmotility and hypotensive patients at risk of developing bowel ischaemia should not receive any fibre, especially insoluble fibre.[4,16] Since bowel dysmotility is present in a great number of ICU patients, the use of most fibre-containing feeds would not be indicated.

In the non-ICU patient population in a general ward or in the long-term home enterally supported patient the scenario can be totally different. Diarrhoea and/or constipation are probably the most commonly encountered complications in these cases. Fibre containing feeds have been shown to be effective in the management of both extremes of stool adaptations and therefore have a definite role to play.[8] To prevent and manage diarrhoea, soluble fibre should be administered and to prevent and manage constipation, a mixture of soluble and insoluble fibre is recommended.[8,9] In the DM patient with gastroparesis, fibre blends, especially insoluble fibre, is not very practical[11] and a high fat intake which normally may have beneficial outcomes on glucose management due to slowing down of gastric emptying, will also worsen the gastroparesis.[20]

References

1. American Diabetes Association Position Statement. Nutrition Recommendations and Interventions for Diabetes. Diab Care 2008;31(suppl 1):S61–S78.
2. Wright J. Total parenteral and enteral nutrition in diabetes. Curr Opin Nutr Metab Care 2000;3:5–10.
3. American Diabetes Association. Standards of Medical Care in Diabetes – 2009. Diab Care 2009;32 (suppl 1):S13–S61.
4. Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition. Crit Care Med 2009;37:1–30.
5. American Diabetes Association. Nutrition recommendations and principles for people with Diabetes Mellitus. Diab Care 1994;17:519–522.
6. American Diabetes Association. Nutrition Principles and Recommendations in Diabetes. Diab Care 2004;27(suppl 1):S36–S46.
7. Franz MJ. Nutritional management of diabetes mellitus and the dysmetabolic syndrome. Clin Nutr Highlights 2006;2:2–7.
8. Meier R & Gassull MA. Consensus recommendations on the effects and benefits of fibre in clinical practice. Clin Nutr Supplements 2004;1:73–80.
9. Alvarez EE & Sanchez PG. Dietary fibre. Nutr Hosp 2006;21(suppl2):60–71.
10. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diab 2008;32(suppl 1):S1–S201.
11. Chen Y & Peterson SJ. Enteral Nutrition Formulas:Which formula is right for your adult patient? Nutr Clin Pract 2009;24:344–355.
12. Cabre E. Fibre supplementation of enteral formula-diets: a look to the evidence. Clin Nutr Supplements 2004;1:63–71.
13. Elia M, et al. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. Aliment Pharmacol Ther 2008;27:120–145.
14. Leon-Sonz M, et al. Glycemic and lipid control in hospital type 2 Diabetic patients. Evaluation of 2 enteral nutrition formulas (Low carbohydrate-High monounsaturated fat vs high carbohydrate). JPEN 2005;29:21 - 29.
15. Hofman Z, et al. Diabetes specific tube feed results in improved glycaemic and triglyceridaemic control during 6 h continuous feeding in diabetes patients. Eur J Clin Nutr Metab 2007;2:44–50.
16. Pohl M, et al;. Glycaemic control in type II diabetic tube-fed patients with a new enteral formula low in carbohydrates and high in monounsaturated fatty acids: a randomised controlled trial. Eur J Clin Nutr 2005;59:1221–1232.
17. Ceriello A, et al. Administration of a new diabetes-specific enteral formula results in an improved 24h glucose profile in type 2 diabetic patients. Diab Research Clin Pract 2009;84:259–266.
18. Crespillo MDC, et al. Metabolic effects of an enteral nutrition formula for diabetes: comparison with standard formulas in patients with type 1 diabetes. Clin Nutr 2003;22:483–487.
19. Elia M, et al. Enteral Nutritional Support and Use of Diabetes-Specific Formulas for Patients with Diabetes. Diab Care 2005;28:2267–2279.
20. Shakil A, et al. Gastrointestinal complications of Diabetes. Am Fam Physician 2008;77:1697–1702.

Micronutrients: do small things matter?

Visser J, BSc Diet, M Nutr
Division of Human Nutrition, Faculty of Health Sciences, Stellenbosch University and Tygerberg Academic Hospital
Correspondence to: Janicke Visser, e-mail: Jconrad@sun.ac.za

Abstract

Despite the major developments on the importance of micronutrient status in health and disease, understanding of the exact role of the latter in critical illness remains elusive and ill defined, complicating decision-making on the part of the nutrition support practitioner. Micronutrient deficiencies in critically ill patients may occur as pre-existing conditions in patients with poor nutritional status prior to hospitalisation or as a result of severe illness or the injury itself. In practical terms it is clear that micronutrients should be provided at, at least, the current available recommended doses to prevent overt clinical deficiencies. For other claims/indications and higher doses the literature consistently indicate that the risk (adverse effects) to benefit (mortality) ratio may be favourable, and if such higher doses are used in practice it should be within the dose range that the current experience covers and for the clinical settings studied only.

S Afr J Clin Nutr 2010;23(1) Supplement:S58-S61

Introduction

It is increasingly and consistently realised that micronutrients have an important role to play in health and disease. Apart from the prevention of clinical deficiency syndromes, the fast developing field of immunonutrition has added yet another dimension to the importance of foods, nutrition and micronutrients in disease prevention and therapy. It is well known that micronutrients are involved in the prevention of nutritional deficiencies, immune humoral and cellular defence, regulation of gene expression during the acute phase response, antioxidant defence and prevention of chronic diseases.[1] Despite these major developments on the importance of other aspects of micronutrient status, understanding of the exact role of the latter in critical illness remains elusive and ill defined, complicating decision-making on the part of the nutrition support practitioner.

In the critical care field it is well-known that nutrition support is a key component of therapy in these patients. Although great care is given to provide adequate and optimal carbohydrate, lipid and protein combinations, the vital role of micronutrients should not be overlooked.[2] Despite the lack of clear guidelines regarding micronutrient requirements in the critically ill, a growing body of evidence (though conflicting at times) is emerging.

Micronutrients in the critically ill patient

Nutritional support of the critically ill patient includes the daily provision of vitamins and trace elements. These compounds, collectively termed "micronutrients", are essential not only as intermediaries in metabolism but also for their potential roles in cellular immunity, wound healing and antioxidant activity.[3] Micronutrient deficiencies in critically ill patients may occur as pre-existing conditions in patients with poor nutritional status prior to hospitalisation or as a result of severe illness or the injury itself.[2] Any injured patient will develop an acute phase response (APR) and a systemic inflammatory response syndrome (SIRS) with the production of various mediators, including cytokines, which modulate the metabolic response.[4,5] SIRS is associated with a redistribution of vitamins and trace elements from the circulating compartment to tissues and organs, which are involved in protein synthesis and immune cell production.[6] The circulating concentrations of most trace elements (iron, selenium, zinc) and of their carrier proteins decrease as do the water-soluble vitamins, whereas copper and manganese increase,[6,7] causing a relative deficit in circulating antioxidants. In addition, trauma and burns patients typically experience extensive loss of biologic fluids through wound exudates, drains and haemorrhage, which contribute to negative micronutrient balances.[5] These deficient states can adversely affect various biochemical processes and enzymatic functions, resulting in organ dysfunction, poor wound healing and altered immune status – all with deleterious patient outcomes.[2] Therefore attention to micronutrient requirements in the critically ill is imperative.

Micronutrients and the oxidative stress state

Oxidative stress has been implicated in the manifestations of critical illnesses, including ischaemia and reperfusion injury and systemic inflammatory states.[8] The latter is increasingly being recognised as vital to the underlying pathophysiology of critical illness, particularly the development of organ failure.[9] Oxidative stress is defined as "a state in which the level of toxic reactive oxygen intermediates (ROI)/reactive oxygen species (ROS) overcomes the endogenous

antioxidant defenses of the host".[8] Oxidative stress can result from either an excess in oxidant production, and/or depletion of antioxidant defenses.[10,11] Protective antioxidant systems help defend against ROS-induced cellular damage. Oxidative stress is thought to increase in the presence of the APR because of the accompanying activation of neutrophils and macrophages and the subsequent release of free radicals,[12] which may overwhelm defensive mechanisms and disturb the pro-oxidant-antioxidant balance in favour of the former, leading to potential damage.[13] Besides ROS, another category of free radicals is derived from nitric oxide (NO) metabolism and is the normal byproduct of endothelial metabolism.[6] Free radicals cause a cascade of intracellular events resulting in the release of nuclear factor-kappa B (NF-Kb) in the cytoplasm,[14] and subsequently enabling the initiation of the transcription process. NF-κB controls the production of acute phase mediators such as tumour necrosis factor (TNF-α), interleukin 2 (IL-2), and IL-2 receptors, which in turn activate NF-κB, intensifying the inflammatory cascade.[6] In this regard, selenium has been shown to downregulate NF-κB, thus limiting the extent of the APR[15,16] whereas antioxidants in general are considered to limit the release of NF-κB caused by ROS.[17] Oxidative stress can cause lipid peroxidation, damage to DNA, and cell death[18] and has been associated with sepsis, shock, mechanical ventilation, organ dysfunction, adult respiratory distress syndrome (ARDS) and surgery.[13]

Thus, critical illness is associated with increased ROS production (and thus increased oxidative stress), and on the other hand low levels of most antioxidant micronutrients (endogenous antioxidant defenses). Good and reliable methods of assessing overall antioxidant status are therefore important, but remain problematic. Measurement of individual micronutrients in the plasma is of limited value, whilst the measurements of total antioxidant capacity (TAC), though promising, have not yet been shown to have sufficient sensitivity or specificity for clinical use.[19] Proof of an increased oxidative stress state is difficult to obtain based solely on measured levels of ROS, due to their short half-life.[11] Evidence for an increased oxidative stress state in critically ill patients is seen indirectly through the measurement of the byproducts of ROS with cellular molecules. These patients demonstrate elevated levels of substances such as thiobarbituric acid-reacting substances (TBARS: byproducts of the interactions of lipids with ROS), DNA and proteins.[2] Oxidative damage markers, such as malondialdehyde (MDA) or F2-isoprostanes, reflect the balance between oxidant stress and the body's ability to cope with it,[20] and are likely to be more useful than antioxidant protection markers in predicting outcome.[21]

Endogenous mechanisms work in a network-like fashion to neutralise the production of ROS in an attempt to counteract the deleterious effects thereof.[2] Intracellular glutathione and nonenzymatic ROS scavengers (including vitamins such as ascorbic acid, β-carotene and α-tocopherol) form part of this highly evolved mechanism. Enzymatic systems [including superoxide dismutase (SOD), catalase and glutathione peroxidases (GSHPx)] then work synergistically to detoxify ROS further. These enzyme systems are dependant on minerals such as selenium, copper, zinc and manganese as important cofactors in these enzymatic reactions.[2]

Of all the antioxidants, special interest is being afforded to selenium as a result of recent supplementation trials. Selenium-dependant enzymes and selenoprotein P regulate immune and endothelial function. Four of the six known glutathione peroxidases play a significant role in antioxidant defenses.[6] The mechanisms involved have been reviewed[22] in detail and indicate that it is not necessarily selenium itself but rather the activity of selenium-dependant enzymes that are of crucial importance.

Micronutrient supplementation in critical illness

Research on micronutrient supplementation in the critically ill has focused mainly on five micronutrients: selenium, zinc, copper, vitamins C and E, and more recently also the vitamin B group.[1,6] The aims of supplementation can be described as provision of basic nutritional support (bearing in mind the increased requirements due to hypermetabolism and wound healing), prevention and correction of deficiencies, and modulation of the APR and immune responses by reinforcement of endogenous antioxidant defences.[1] Establishing requirements in the critically ill has proven notoriously difficult and various sets of guidelines (each with their own limitations in a particular population) and proposals from various authors are available.[5,23-29]

Despite these guidelines and proposals little consensus exists as to "what to use when" and many questions remain regarding doses required, route and timing of replacement. It is also imperative to bear in the mind the potential for deleterious effects, i.e. "more is not necessarily better". Micronutrients, especially trace elements and fat soluble vitamins, carry the risk of toxicity at high intake levels.[5,6] Nutrition support practitioners considering supplementing antioxidant micronutrients in critically ill patients should proceed with caution and consider the amounts of such micronutrients a patient is already receiving through an oral diet and/or enteral/parenteral nutritional support. Inappropriate antioxidant micronutrient supplementation has the potential for creating a pro-oxidant microenvironment that may have as much potential for harm as for benefit in the well-nourished patient.

A growing body of evidence is emerging that demonstrates the potential benefits of micronutrient (and specifically antioxidant) supplementation in critically ill patients.

Synthesis of the evidence

Despite two published systematic reviews already available in the literature,[9,30] the sum-total of available evidence (including the outcome of these two meta-analyses) still indicates that the exact micronutrient requirements of the critically ill patient and related practice issues remain uncertain. Since the systematic review by Heyland et al[9] was published in 2005, several trials were conducted (including larger multi-centre trials) prompting our group to explore the questions once more by aggregating the latest trial data and results with those of the older trials, with the aim of obtaining better clarity and further answers.[31]

The systematic review and meta-analysis undertaken by our group[31] substantially builds on the initial very important review by Heyland et al[9] by including seven new trials, including the first four multi-centre randomised controlled trials in this area of research.[32-35] This updated review[31] indicates and supports previous findings[9] that micronutrient supplementation in the critically ill may be associated with a reduction in overall mortality, and specifically 28 day mortality.

Table I: Recommended doses and doses used in RCTs of selected micronutrients in critical illness

Micronutrient (MN)	RDA for oral feeding (daily)[23,24]	UL[40,41]	Recommendations for PN			Proposed supplements (in addition to MNs provided by feeding)			Doses in RCTs
			AMA 1979[25,26]	Shenkin 1995[27]	FDA 2000[28]	Berger 2006[5]		Fuhrman 2002 (/d)[29]	
						Major trauma (5d)	Major burns (14-21d)		
Vitamin C (mg)	60	2000	100	100	200	1000 (IV)	1000 (IV)	500-3000	500-3000 (IV) 133-500 (EN)
Vitamin E (mg)	8–10	1000	10	10	10	100 (EN)	100 (EN)	400 (IV) 40–1000 (EN)	50-400 (IV) 50-1350 (EN)
Selenium (µg)	55–70	400	30–60	60	-	300 (IV)	500 (IV)	100–400	200-4000 (IV)
Zinc (mg)	12–15	40	2.5–4	6.5	-	20 (IV)	30 (IV)	10–30	12-37.5 (IV)
Copper (mg)	2	10	0.5–1.5	1.3	-	-	4 (IV)	-	2.5-3.75 (IV)

AMA: American Medical Association; d: day; EN: Enteral nutrition; FDA: Food and Drug Administration; IV: Intravenous; MN: Micronutrient; PN: Parenteral nutrition; RCT: Randomised controlled trial; RDA: Recommended dietary allowance for healthy people; UL: Tolerable upper intake level (general population)

Micronutrient supplementation in the updated systematic review[31] was not associated with a reduction in infectious complications, similar to the findings of Heyland et al.[9] This finding could possibly indicate that the mortality effect observed was mediated by other mechanisms (e.g. improved organ function). The updated review[31] was the first to report on LICU and LOS and found that these outcomes were unaffected by micronutrient supplementation.

In sub-group analyses of the updated review,[31] single nutrients were associated with borderline statistical significance ($p = 0.06$) in terms of mortality, whilst a sensitivity analysis of combined micronutrients indicated a significant reduction in mortality ($p = 0.006$). Although in contrast to the Heyland et al[9] findings (i.e. single nutrients were associated with a significant reduction in mortality; combined micronutrients were not), the findings of the updated review would appear to support prior hypotheses and the rationale underlying the use of combinations of micronutrients, based on observations of the biochemical properties of the endogenous antioxidant network and the fact that micronutrients depend on each other for regeneration in a continued spiral.[1]

The updated review did not find clear evidence that parenteral is superior to enteral administration in terms of clinical outcomes, in contrast to the Heyland et al[9] review that did find a significant reduction in mortality associated with parenteral administration of antioxidants. The vast majority of trials available in the literature delivered micronutrients intravenously, with the intravenous route seen as the only reliable method by which micronutrients can be administered in the critically ill.[2] Absorption by the enteral route in critically ill patients is unpredictable due to bowel oedema, bowel ischaemia, haemodynamic instability, fluid resuscitation and alterations in blood supply.[36] On the other hand, delivering micronutrients to the gut may be beneficial through the attenuation of the local gut inflammatory response,[37] indicating that both routes, theoretically at least, do have their advantages.[9] Given the major role of the gastrointestinal tract as a source of cytokine and leukocyte activation and ROS formation, the provision of key nutrients directly to the gastrointestinal tract makes biological sense.[38] It is thus proposed that future studies investigate the use of both parenteral and enteral administration of micronutrients to maximise the opportunity of demonstrating a treatment effect, if one truly exists.

The current evidence and updated review confirms that timing, duration and dosing are key factors to ensure optimal clinical benefit. The timing of micronutrient supplementation is important and is probably a key factor as the repletion of micronutrients, and specifically antioxidants, would probably achieve a greater efficacy if given before massive oxidative injury (e.g. severe sepsis or septic shock).[39] Despite the fact that no studies could be found comparing early to late micronutrient supplementation in the critically ill, it is reasonable to conclude that micronutrient supplementation should begin early in the course of critical illness to offset the deleterious effects of ROS. Another important factor to consider is the duration of supplementation, which should be sufficient to produce optimal clinical benefit.

In terms of micronutrient doses (Table I) the updated systematic review[31] has highlighted the fact that there is still not clarity regarding optimal doses and which patients will benefit most (or will be adversely affected), and that further large multi-centre trials (including dose-finding trials) are necessary. It is of obvious importance to find the optimal dose for micronutrients administration, which is effective without producing a pro-oxidant effect.

Importantly, the vast majority of trials avaiable in the literature reported no adverse/deleterious effects of micronutrient administration, with the exception of one trial that deserves mention.[35] This study by Siriwardena et al,[35] conducted in patients with severe acute pancreatitis, indicated a trend towards worse outcome in the treatment arm of the study (although results were not statistically significant and not demonstrably treatment related). The outcome of this study warrants caution, at least in patients with severe acute pancreatitis. In general terms, practitioners will be well served by remembering "more is not necessarily better". Micronutrients may have dose-response curves with toxicity risk at high levels of intake. Zinc toxicity has been reported with doses of over 50 mg per day[42]

and an upper limit of intake of selenium in the diet has been set at 400 µg (5 µg/kg) per day (although a no observable effect level of 800 µg per day has been proposed).[24] An upper limit for safe short-term intravenous supplementation of 750-1000 µg selenite per day in the critically ill has been suggested[22] with a dose of 800 µg of selenium per day given via the combined IV and enteral route documented to be safe in a dose-finding study.[43] Results of a meta-analysis of 19 RCTs in the community suggest that high dosages of vitamin E increase risk of all-cause mortality, and this dose-dependant increase begins at 150 IU/day.[44] It is not clear to what extent all these considerations apply to the critically ill, but certainly should warrant a word of caution. More dose-finding trials are therefore required to establish optimal doses.

Conclusions

The current evidence does suggest potential benefit of micronutrient supplementation in critically ill adults in terms of some clinical outcomes, but also highlights that caution is warranted in terms of micronutrients administered, doses and specific patient populations targeted as nutrient interactions and risk of toxicity are not clearly defined in critical illness. Once more the conclusion is that there is a need for more large multi-centre prospective randomised controlled trials to assess the effects of different types and doses of micronutrient supplementation in selected groups of patients with different types of critical illness, with a few such trials already underway.[38,45] It has been suggested that targeting the appropriate patient populations most likely to benefit (i.e. the more severely ill patients), considering the route of delivery (possibly a combination of parenteral and enteral) as well as attention to doses administered might maximise the opportunity of demonstrating a treatment effect, if one truly exists. In practical terms it is clear that micronutrients should be provided at, at least, the current available recommended doses to prevent overt clinical deficiencies. For other claims/ indications and higher doses the literature consistently indicates that the risk (adverse effects) to benefit (mortality) ratio may be favourable, and if such higher doses are used in practice it should be within the dose range that the current experience covers and for the clinical settings studied only.

References:

1. Berger MM, Chioléro. Key vitamins and trace elements in the critically ill. Nestle Nutr Workshop Ser Clin Perform Programme. 2003;8:99-111; discussion 111-7.
2. Sriram K, Cué JI. Micronutrient and antioxidant therapy in critically ill patients. In: Cresci G, editor. Nutrition support for the critically ill patient. New York: Taylor & Francis, CRC Press; 2005:109-123.
3. Prelack K, Sheridan RL. Micronutrient supplementation in the critically ill patient: strategies for clinical practice. J Trauma 2001;51(3):601-620.
4. Cartwright MM. The metabolic response to stress: a case of complex nutrition support management. Crit Care Nurs Clin N Am 2004;16(4):467-487.
5. Berger MM. Antioxidant micronutrients in major trauma and burns: evidence and practice. Nutr Clin Pract 2006;21(5):438-449.
6. Berger MM, Shenkin A. Update on clinical micronutrient supplementation studies in the critically ill. Curr Opin Clin Nutr Metab Care 2006;9(6):711-716.
7. Galloway P, McMillan DC, Sattar N. Effect of the inflammatory response on trace element and vitamin status. Ann Clin Biochem 2000;37:289-297.
8. Bulger EM, Maier RV. Antioxidants in critical illness. Arch Surg 2001;136:1201-1207.
9. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med 2005;31(3):327-337.
10. Goodyear-Bruch C, Pierce JD. Oxidative stress in critically ill patients. Am J Crit Care 2002;11(6): 543-551.
11. Lovat R, Preiser JC. Antioxidant therapy in intensive care. Curr Opin Crit Care 2003;9:266-270.
12. Goode HF, Webster NR. Free radicals and antioxidants in sepsis. Crit Care Med 1993;21:1770-1776.
13. Oldham KM, Wise SR, Chen L, Stacewicz-Sapuntzakis M, Burns J, Bowen PE. A longitudinal evaluation of oxidative stress in trauma patients. J Parenter Enteral Nutr 2002;26:189-197.
14. Flohe´ L, Brigelius-Flohe´ R, Saliou C, et al. Redox regulation of NF-kappa B activation. Free Rad Biol Med 1997;22:1115-1126.
15. Kim SH, Johnson VJ, Shin TY, Sharma RP. Selenium attenuates lipopolysaccharide-induced oxidative stress responses through modulation of p38 MAPK and NF-kappa B signaling pathways. Exp Biol Med (Maywood) 2004;229:203-213.
16. Kretz-Remy C, Arrigo AP. Selenium: a key element that controls NF-kappa B activation and I kappa B alpha half life. Biofactors 2001;14:117-125.
17. Berger MM, Chioléro R. Energy, trace element and vitamin requirements in major burns. Critical Care Shock 2002;2:91-103.
18. Sardesai VM. Role of antioxidants in health maintenance. Nutr Clin Pract 1995;10:19-25.
19. Roth E, Manhart N, Wessner B. Assessing the antioxidative status in critically ill patients. Curr Opin Clin Nutr Metab Care 2004;7:161-168.
20. Evans P, Halliwell B. Micronutrients: oxidant/antioxidant status. Br J Nutr 2001;85 (Suppl 2):S67-S74.
21. Mishra V, Baines M, Wenstone R, Shenkin A. Markers of oxidative damage, antioxidant status and clinical outcome in critically ill patients. Ann Clin Biochem 2005;42:269-276.
22. Angstwurm MW, Gaertner R. Practicalities of selenium supplementation in critically ill patients. Curr Opin Clin Nutr Metab Care 2006;9:233-238.
23. Subcommittee on the 10th RDAs Edition on Recommended Dietary Allowances. 10th ed. Washington, DC: National Academy Press; 1989.
24. Food and Nutrition Board of the Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. Washington, DC: National Academy Press; 2000.
25. Shils ME, Burke AW, Greene HL, Jeejeebhoy KN, Prasad AS, Sandstead HH. Guidelines for essential trace element preparations for parenteral use. A statement by an expert panel. AMA Department of Foods and Nutrition. J Am Med Assoc 1979;241:2051-2054.
26. American Medical Association. Department of Foods and Nutrition. Multivitamin preparations for parenteral use. A statement by the Nutrition Advisory Group. J Parenter Enteral Nutr 1979;3:258-262.
27. Shenkin A. Adult micronutrient requirements. In: Payne-James J, Grimble G, Silk D, editors. Artificial nutrition support in clinical practice. London, England: Edward Arnold Publishers; 1995:151-166.
28. Food and Drug Administration (FDA). Parenteral multivitamin products: Drugs for human use; Drug efficacy study implementation, Amendment. Federal Register, 2000;65 (77):21200-21201, 2000.
29. Fuhrman PM, Herrmann VM. Micronutrients in critical illness. In: Shikora SA, Martindale RG, Schwaitzberg SD, editors. Nutritional considerations in the intensive care unit. American Society for Parenteral and Enteral Nutrition, Silver Springs, MD; 2002:51-60.
30. Avenell A, Noble DW, Barr J, Engelhardt T. Selenium supplementation for critically ill adults. Cochrane Database Syst Rev 2004;18;(4):CD003703.
31. Visser J, Labadarios D, Blaauw R. Micronutrient supplementation for critically ill adults: a systematic review and meta-analysis. 2008. (Unpublished data)
32. Angstwurm MW, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med 2007;35(1):118-126.
33. Crimi E, Liguori A, Condorelli M, Cioffi M, Astuto M, Bontempo P, et al. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. Anesth Analg 2004;99(3):857-863.
34. Forceville X, Laviolle B, Annane L, Vitoux D, Bleichner G, Korach JM, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. Crit Care 2007;11(4):R73.
35. Siriwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, et al. Randomized, double blind, placebo controlled trial of intravenous antioxidant (n-acetylcysteine, selenium, vitamin C) therapy in severe acute pancreatitis. Gut 2007;56:1439-1444.
36. Berger MM, Berger-Gryllaki M, Wiesel PH, Hurni M, Revelly JP, Tappy L, et al. Gastrointestinal absorption after cardiac surgery. Crit Care Med 2000;28:2217-2223.
37. Deitch EA, Adams C, Lu Q, Xu DZ. A time course study of the protective effect of mesenteric lymph duct ligation on hemorrhagic shock-induced pulmonary injury and the toxic effects of lymph from shocked rats on endothelial cell monolayer permeability. Surgery 2001;129:39-47.
38. Heyland DK, Dhaliwal R, Day AG, Muscedere J, Drover J, Suchner U, et al. REducing Deaths due to OXidative Stress (The REDOXS Study): rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. Proc Nutr Soc 2006;65:250-263.
39. Mishra V. Oxidative stress and role of antioxidant supplementation in critical illness. Clin Lab 2007;53(3-4):199-209.
40. Institute of Medicine. Dietary Reference Intakes for vitamin C, vitamin E, selenium and carotenoids. Food and Nutrition Board. Washington DC. National Academy Press. 2000
41. Institute of Medicine. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Food and Nutrition Board. Washington DC. National Academy Press. 2001.
42. Sandstead HH. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. Am J Clin Nutr 1995;61(3):S621-S624.
43. Heyland DK, Dhaliwalm R, Day A, Drover J, Cote H, Wischmeyer P. Optimizing the dose of glutamine dipeptides and antioxidants in critically ill patients: a phase I dose-finding study. J Parenter Enteral Nutr 2007;31(2):109-118.
44. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46.
45. Andrews PJ, Avenell A, Noble DW, Campbell MK, Battison CG, Croal BL, et al. for The Trials Management Group. Randomised trial of glutamine and selenium supplemented parenteral nutrition for critically ill patients. Protocol Version 9, 19 February 2007 known as SIGNET (Scottish Intensive care Glutamine or seleNium Evaluative Trial). Trials 2007;8(1):25-39.

Nutritional management of gastrointestinal malignancies

Smalberger R, MSc Diet (UFS), RD(SA)
Correspondence to: René Smalberger, e-mail: kien@mweb.co.za

Abstract

The evidence connecting food and gastrointestinal cancers from epidemiological studies, case-control studies, and prospective observational studies, indicates that determining the independent effects of specific nutrients is extremely difficult, given the many potential environmental factors to consider. The nutritional management of a patient with gastrointestinal cancer first begins with an appropriate nutritional assessment, seeing that several factors could affect the patient's nutritional status. The most significant dietary advice for cancer patients in general, is to consume a significant amount of energy daily to maintain current body weight, as well as a liberal amount of protein. In cancer patients requiring gastrointestinal surgery, the benefit of delaying surgery to attain improved nutritional status needs to be determined for improved outcomes. Postoperatively, severely malnourished cancer patients, and patients with an anticipated inadequate nutritional intake for seven days or longer, will benefit from postoperative TEN, given within 48 hours after surgery. Regular monitoring and adjustments to nutritional prescriptions is imperative in order to improve the cancer patient's nutritional status within the context of the prognosis.

S Afr J Clin Nutr 2010;23(1) Supplement:S62-S64

The evidence connecting food and gastrointestinal malignancies from epidemiological, case-control, and prospective observational studies, indicate that determining the independent effects of specific nutrients is extremely difficult, given the many potential environmental factors to that need to be considered.[1–3]

Nevertheless some associations have been documented. For instance, oesophageal cancer has been linked to low intakes of vitamin C, selenium and zinc, with a protective effect been afforded by an increased fruit and vegetable intake. Meat and fish consumption has shown inconsistent associations with oesophageal cancer studies.[1]

Gastric cancer has been linked to foods preserved with salt or foods with a high salt content, while fruit and vegetable intake has been shown to have a protective effect against gastric cancer. Green tea has shown a protective effect against gastric cancer in several studies.[4] Japanese studies have shown a strong environmental factor in the development of gastric cancer.[5] Pancreatic cancer has been linked to increased energy intake and obesity.[1] Dietary fat,[6,7,8] increased energy intake,[9,10,11] processed meats,[12] and central obesity appear to increase the risk of colon cancer in some studies.

Nutritional assessment

Nutritional management of a patient with gastrointestinal malignancy first begins with an appropriate nutritional assessment, since several factors could affect the patient's nutritional status. Long standing nutritional deficiencies could result in compromised cellular immunity which causes an increased risk for infection and delayed wound healing after surgery. Patients with the potential to become malnourished should be identified as early as possible during the treatment process. Nutritional management of these frail patients should be goal orientated, trying to correct nutritional deficiencies. It is important to realise that nutritional status will also be affected by underlying comorbidities that may increase the patient's risk for nutritional deficits.[1]

Assessing the patient's general nutritional status at the start of treatment is imperative.[13,14] A complete medical and dietary history is probably the best tool to achieve this goal . The important factors to assess include dietary and physical examination, anthropometrics and laboratory parameters which may reflect nutrient deficits. Patients that have lost a significant amount of weight, greater that 10% of initial body weight, and have shown a reduced oral energy intake for a period of between two and 24 weeks are at greater risk of developing both macronutrient and micronutrient deficiencies. Available evidence indicates that cancer patients with a weight loss greater that 10% of their initial body weight have a reduced appetite, lower chemotherapy response as well as shorter medial survival time.[15] The Subjective Global Assessment (SGA) is a clinical method that can be used for the evaluation of a patient's nutritional status. The SGA is a reliable tool to use in clinical settings, with an 80% accuracy.[16]

The most significant dietary advice for cancer patients in general, is to consume an adequate amount of energy daily in order to maintain current body weight, as well as a liberal amount of protein. Oral energy intake should be approximately 105–150 kJ/kg/day. A protein intake of approximately 1,0–1,5 g/kg/day will be adequate to meet the requirements of most non-wasted cancer patients. Cancer patients with a weight loss greater than five percent of their initial body weight should be advised to increase their daily energy intake by an additional 2100 KJ over and above the recommended intake of 105–150 kJ/kg/day. In such patients, protein intake should be maximised at 1,5 g/kg/day. It is also important to keep in mind that due to the malignancy induced inflammatory response in advanced cancer, additional energy and protein intake may not improve lean muscle mass.[1]

Gastrointestinal surgery

Surgery is the treatment of choice in patients with cancer of the oesophagus, with radiation and chemotherapy often given pre-operatively. Side effects of radiation and chemotherapy often result in further weight loss. Surgical treatment usually involves a total or distal oesophagectomy requiring bilateral vagotomy, proximal gastrectomy, and anastomosis of the retained portion of the oesophagus to the remaining stomach. Post-operative regurgitation of food and bloating are common complications following surgery that can result in further weight loss and debilitation. Oesophageal strictures can appear post-operatively that often require repeated dilatation to ensure adequate food passage. Placing an oesophageal stent to improve food and fluid passage may be a palliative measure for non-surgical patients who experience severe dysphasia due to oesophageal luminal cancer growth.[1,17]

Nutrition support of gastrointestinal cancers

In cancer patients requiring gastrointestinal surgery, the benefit of delaying surgery to attain improved nutritional status needs to be carefully considered. Nutritional support can be given by either intravenous [parenteral nutrition (PN)] or total enteral nutrition (TEN). Available literature suggests that severely malnourished cancer patients, with a weight loss greater than 10% of their initial body weight, will benefit from preoperative TPN for a duration of seven to ten days.[18] Although improved mortality has not been reported with improved nutritional status, a 10% improvement in postoperative complications has been reported in nutritionally supported patients when compared to patients who had nutrition support. Administration of PN pre-operatively to non-malnourished patients is not recommended, as it results in increased PN associated complications.[19] Nutritional support of the hospitalised cancer patient should be commenced as soon as nutritional intake does not match daily increased requirements for a period longer than seven days. After a fasting period of seven to ten days, a negative nitrogen balance is known to occur, which increases the patient's risk for infections and interferes with wound healing. The practicality of giving PN for seven to ten days prior to surgery is however often a problem.[1]

Postoperatively, severely malnourished cancer patients, and patients with an anticipated inadequate nutritional intake for seven days or longer, will benefit from postoperative TEN, given within 48 hours after surgery.[18] Nutritional improvement appear to be more significant with TEN compared to TPN post surgery.[20] Patients with a pre-operative weight loss greater that 10% of initial body weight should ideally have a jejunal feeding tube place at the time of surgery. The feeding tube can later be removed as an outpatient, once normal oral intake has resumed.

Early satiety, postprandial abdominal pain and weight loss are frequently experienced by patients with gastric cancer. Surgical resection usually requires a total gastrectomy with an oesophageal anastomosis. Significant weight loss; dumping syndrome; fat malabsorption; and iron, calcium and vitamin B12 deficiency commonly occur postoperatively. Fluid nutritional supplements and small frequent meals may be beneficial to post-surgical patients with dumping and bloating. Increasing the pectin content in the diet to slow down gastric emptying and minimise fall in postprandial blood glucose levels is helpful and improves the nutritional management of such patients.[21] Steatorrhea may occur due to secondary pancreatic insufficiency, and could be treated with pancreatic enzyme supplementation.[22] Vitamin and mineral deficiencies should be prevented and treated with adequate oral supplementation of iron, vitamin C and B12. Nocturnal jejunal feeding should be considered in patients who continue to lose weight despite dietary adjustments/supplements.[1]

Treatment of colorectal cancer involves resection of the affected segment of the bowel. Postoperative chemotherapy is usually tolerated well, with few nutrition-related side effects. If large sections of the right colon are resected, and the ileocaecal valve is compromised, postprandial diarrhoea may result. If more than 60 cm of the terminal ileum is resected, vitamin B12 supplementation will be necessary.[1]

Parenteral nutrition

Indications for parenteral nutrition include small bowel obstruction, which may develop due to tumour growth; severe diarrhoea and malabsorption during the active treatment of the disease; gastrointestinal haemorrhage; treatment of fistulae; and as a supportive care for severely malnourished patients. PN is not generally indicted for patients with non-obstructive disease or if the duration for nutritional support is suspected to be shorter than seven days. There is no evidence to support that PN improves the outcome of chemotherapy or radiation-related treatment or the survival of patients with cancer.[23] Optimal nutrition does however affect the patient's quality of life.

Peripheral parenteral nutrition can be used when short-term nutritional support is needed for a period of less than seven to ten days.[1]

How much?

Several studies have investigated energy expenditure and protein needs of cancer patients. Cancer patients with active disease may require as much as 1,2–1,5 times increased energy intake compared to normal resting energy expenditure. Energy needs can be calculated up to 168 kJ/kg/day of ideal body weight, and 1–1,5 g/kg of ideal body weight for protein are usually sufficient for most adult cancer patients. Most hospitalised cancer patients only require nutritional support for up to two weeks.[1]

Monitoring safety

PN will not have any significant value to the patient if not used and monitored appropriately. Monitoring the therapy and making regular adjustments as required is imperative to achieve the desired goal/benefit. Patients should be weighed daily, and accurate fluid intake and output should be recorded. Urine output should be more than 1000 ml per 24 hours in order to ensure adequate hydration of the patient. A weight gain of more than one to two kilograms per week usually indicates fluid retention. This may occur in the first two weeks after PN is initiated. Diuretic therapy is occasionally required. Electrolytes and triglyceride levels should be monitored twice weekly.[24]

The human body adapts to weight loss and starvation by reducing resting energy expenditure. When large amounts of energy and carbohydrates are supplied to a malnourished cancer patient at too rapid a pace, refeeding syndrome may result.[25] Refeeding is a potentially life-threatening complication of both PN and TEN when carbohydrate intake stimulates pancreatic insulin release, which results in the flow of potassium and magnesium to the intercellular space, with the possibility of cardiac arrhythmias as an adverse outcome. Prevention of refeeding syndrome is possible by using a mixed carbohydrate, protein and lipid formula, and gradually increasing the rate of administration.

Enteral nutrition

Enteral nutrition is recommended in the absence of bowel obstruction, high output fistula, or toxic megacolon. Because of postoperative gastroparesis, jejunal feeding may be preferred for specific cancer patients. TEN is generally started at a relatively slow rate (40 ml/h) and gradually increased eight hourly until the nutritional goal is reached. In severely malnourished patients, the infusion rate may have to be started at an even slower rate so as to avoid the refeeding syndrome. No standard commercial formula provides sufficient free water to meet the patient's daily fluid requirements. Small frequent bolus amount of free water is required to meet patient needs.[1] Percutaneous endoscopic gastroscopy (PEG) feeding is often an effective and emotionally acceptable means of long term TEN.

Regular monitoring and adjustments to nutritional prescriptions is imperative in order to achieve nutritional goals which will improve the patient's nutritional status.

References

1. Scolapio JS, Buchman AL. 2005. Gastrointestinal Cancer: Diagnosis and Management Issues, In The Clinician's Guide to Gastrointestinal Oncology. Ed. by M Kockman. Thorofare: SLACK Incorporated, pp.307–27.
2. Hensrud DD, Heimburger DC. 1998. Diets, Nutrients, and Gastrointestinal Cancer. Gastroenterol Clin North Am. vol.27, **no.2, pp.325–46**.
3. Silverman DT, Swanson CA, Gridley G, et al. 1998. Dietary and Nutritional Factors and Pancreatic Cancer: a Case Control Study Based on Direct Interviews. J Natl Cancer Inst. vol.90, **no.22, pp.1710–9**.
4. Kono S, Hirohata T. 1996. Nutrition and Stomach Cancer. Cancer Causes Control. vol.7, **no.1, pp.41–55**.
5. Haenszel W, Kurihara M. 1968. Studies from Japanese Migrants. I. Mortality from Cancer and Other Diseases Among Japanese in the United States. J Natl Cancer Inst. vol.40, **no.1, pp.43–68**.
6. Schatzkin A, Lanza E, Corle D, et al. 2000. Lack of Effect of a Low-Fat, High-Fiber Diet on the Recurrence of Colorectal Adenomas. Polyp Prevention Trial Study Group. N Engl J Med. vol.342, **no.16, pp.1149–55**.
7. MacLennan R, Macrae F, Bain C, et al. 1995. Randomized Trial of Intake of Fat, Fiber and Beta Carotene to Prevent Colorectal Adenomas. J Natl Cancer Inst. vol.87, **no.23, pp.1760–6**.
8. McKeon-Eyssen GE, Bright-See E, Bruce WR, et al. 1994. A Randomized Trial of a Low Fat High Fiber Diet in the Recurrence of Colorectal Polyps. Toronto Polyps Prevention Group. J Clin Epidemiol. vol.47, **no.5, pp.525–36**.
9. Goldbohm RA, Van der Brandt PA, van't Veer P, et al. 1994. A Prospective Cohort Study on the Relation between Meat Consumption and the Risk of Colon Cancer. Cancer Res. vol.54, **no.3, pp.718–23**.
10. Armstrong B, Doll R. 1975. Environmental Factors and Cancer Incidence and Mortality in Different Countries, with Special Reference to Dietary Practices. Int J Cancer. vol.15, **no.4, pp.617–31**.
11. Giovannucci E, Rimm EB, Stampfer ME, et al. 1994. Intake of Fat, Meat and Fiber in Relation to Risk of Colon Cancer in Men. Cancer Res. vol.54, **no.9, pp.2390–7**.
12. Sandhu MS, White IR, McPherson K. 2001. Systematic Review of the Prospective Cohort Studies on Meat Consumption and Colorectal Cancer Risk: a Meta-Analytical Approach. Cancer Epidemiol Biomarkers Prev. vol.10, **no.5, pp.439–46**
13. **Repetto L, Fratino L, Audisio RA, et al. 2002. Comprehensive Geriatric Assessment Adds Information to Eastern Cooperative Oncology Group Performance Status in Elderly Cancer Patients: An Italian Group for Geriatric Oncology Study. J Clin Oncol.** vol.15, **no.20, pp.494–502**.
14. Pope D, Ramesh H, Gennari R, et al. 2006. Pre-Operative Assessment of Cancer in the Elderly (PACE): A Comprehensive Assessment of Underlying Characteristics of Elderly Cancer Patients Prior to Elective Surgery. Surg Oncol. vol.15, **no.46, pp.189–97**.
15. Dewys WD, Begg C, Lavin PT, et al. 1980. Prognostic Effect of Weight Loss Prior to Chemotherapy in Cancer Patients. Eastern Cooperative Oncology Group. Am J Med. vol.69, **no.4, pp.491–7**.
16. Detsky AS, McLaughlin JR, Baker JP, et al. 1987. What is Subjective Global Assessment of Nutritional Status. J Parenter Enter Nutr. vol.11, **no.1, pp.8–13**.
17. Audisio RA, Ramesh HS, Sestini A, et al. 2008. Shall we Operate? Preoperative Assessment in Elderly Cancer Patients (PACE) can help. A SIOG Surgical task Force Prospective Study. Crit Rev Oncol Hematol. vol.65, **no.2, pp.156–63**.
18. Satyanarayana R, Klein S. 1998. Clinical Efficacy of Perioperative Nutrition Support. Curr Opin Clin Nutr Metab Care. vol.1, **no.1, pp.51–8**.
19. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative Total Parenteral Nutrition in Surgical Patients. 1991. N. Engl J Med. vol.325, **no.8, pp.525–32**.
20. Bozetti F. 2001. Nutrition in Gastrointestinal Cancer. Curr Opin Clin Nutr Metab Care. vol.4, **no.6, pp.541–6**.
21. Jenkins DJ, Bloom SR, Albuquerque RH, et al. 2001. Pectin and Complications After Gastric Surgery: Normalisation of Postprandial Glucose and Endocrine Responses. Gut. vol.21, **no.7, pp.574–9**.
22. Hinw RJ, Srivastava S, Milner JA, Ross SA. 2003. Nutritional Links to Plausible Machanisms Underlying Pancreatic Cancer: A Conference Report. Pancreas. vol.27, **no.4, pp.356–66**.
23. Scolapio JS, Ukleja A, Burnes JU, Kelly DG. 2002. Outcome of Patients with Radiation Enteritis Treated with Home Parenteral Nutrition. Am J Gastroenterol. vol.97, **no.3, pp.662–6**.
24. Toskes PP. 1990. Hyperlipidemic Pancreatitis. Gastroenterol Clin North Am. vol.19, **no.4, pp.783–91**.
25. Solomon SM, Kirby DF. 1990. The Refeeding Syndrome: A Review. J Parenter Enteral Nutr. vol.14, **no.1, pp.90–7**.

The gastrointestinal tract and HIV pathogenesis

Downs JH
Dietetics Departtment, King Edward VIII Hospital, Durban, South Africa
Correspondence to: Me Jane Downs, e-mail: jane.downs@kznhealth.gov.za

Abstract

Gastrointestinal dysfunction has been recognised as a major manifestation of the human immunodeficiency virus (HIV) infection usually presenting as diarrhoea which may or may not be due to the presence of an opportunistic infection of the GIT. Contrary to earlier assumptions, there is now substantial evidence to demonstrate that there are significant changes in the gut in the acute phase of HIV infection; the most significant of these being the substantial loss of the CD4+ T-cells in the GIT. Delays in the initiation of HAART (that is, once the CD4+ T-cell count drops below 200 cells/uL), is associated with a greater severity of HIV-associated GIT enteropathy, and poor clinical outcome.

S Afr J Clin Nutr 2010;23(1) Supplement:S65-S68

Introduction

Gastrointestinal dysfunction has been recognised as a major manifestation of the human immunodeficiency virus (HIV) infection since the earliest recognition of the syndrome, the acquired immune-deficiency syndrome (AIDS). It was originally thought that these disease manifestations were the sequelae of the immune destruction which characterises AIDS, rather than it being central to the pathogenesis of AIDS. In the past decade, it has been observed that the mucosal immune system and the intestinal immune system are pivotal in the pathogenesis of AIDS, with the most critical events, namely transmission, viral amplication, and $CD4^+$ T-cell destruction occurring in the gastrointestinal tract (GIT). Furthermore, the breakdown of the mucosal barrier with consequent microbial translocation, are considered to be major drivers of AIDS progression.[1] In this regard, the GIT mucosal tissue is not only a primary site of viral transmission, but also a major site of viral replication, $CD4^+$ T-cell destruction, regardless of the route of transmission.[1]

HIV enteropathy

GIT enteropathy in persons living with HIV (PLWH) can occur from the acute phase of infection, through to advanced disease. It is characterised by diarrhoea, increased GIT inflammation, increased intestinal permeability (up to fivefold higher than in healthy individuals), malabsorption of bile acids, and vitamin B_{12}. Histologically, the GIT enteropathy in HIV involves inflammatory infiltrates of lymphocytes and damage to the GIT epithelial layer (which includes villous atrophy, crypt hyperplasia and villous blunting). These pathological changes may occur in the absence of any detectable bacterial, viral or fungal enteropathogens, which are often associated with enteropathy.[2] HIV enteropathy was reported as early as 1984.[3]

Although the mechanism(s) that cause the abnormalities in HIV enteropathy, are poorly understood, it has been suggested that HIV has a direct "virotoxic" effect on the enterocyte. It has been observed that the HIV accessory protein Tat has an inhibitory effect on glucose uptake in the enterocyte. HIV gp120 has been found to result in increased concentrations of calcium in the enterocyte, which is associated with tubulin depolymerisation, and a decrease in epithelial cells' ability to maintain ionic balances. It has also been postulated that HIV may result in abnormal differentiation of the enterocyte, as it has been found to be in the proximity of abnormally enlarged enterocytes.[2]

Local activation of the GIT immune system is also thought to play a role in HIV enteropathy. In HIV there are high levels of proinflammatory mediators such as beta chemokines interleukin-6 (IL-6), interleukin-10 (IL10) and interferon (IFN-γ) found in the lamina propria of the colon in PLWH. The degree of inflammation has been found to correlate with the level of viral replication. Although systemic immune activation is a hallmark of HIV, the aetiology of the latter remains elusive. It has also been postulated that local bacterial translocation across the damaged tight epithelial barrier, results in microbial products that stimulate the immune system locally, presumably through receptors such as Toll-like receptors. A crucial consequence of induction of local inflammation through any means, is through HIV's preferential infection of activated $CD4^+$ T-cells, which in turn augments the HIV replication.[2]

CD4+ T-cell destruction

Originally it was thought that HIV involved a period of latency, however, it is now well established that the HIV virus attaches to the CD4+ molecule on the T-cells and the monocyte and macrophage lineage cells, and on a chemokine receptor, during acute infection. The direct infection of CD4+ T-cells leads to the destruction of these cells and global immune deficiency, as these cells are required for induction and control of most immune responses. The infection of the monocyte and macrophage lineage cells appears to be particularly important in chronic HIV infection and are possibly major reservoirs for viral replication and persistence, and hence contributing to immune deficiency.[1]

More recently, it has been observed that the CD4+ T-cells which bear the CCR5 HIV co-receptor are the primary targets of HIV. The CD4+ T-cells with CCR5 receptors constitute the majority of the CD4+ T-cells. It is estimated that nearly eighty percent of the T-cell population is found in the GIT.[3]

Depletion of the CD4+ T-cells involves the entire GIT.[2] The largest number of mucosal memory CD4+ T-cells are found in the GIT, and significant depletion of these cells occurs in the first 17 days post HIV infection. In a recently postulated model (based on GIT biopsies), it is thought that the bulk of CD4+ T-cell depletion occurs in the first two to three weeks of acute infection.[3]

PLWH with a CD 4 count of less than 200 cells/uL, have been found to have a twofold increase in diarrhoea. The latter affirms the view that diarrhoea is an AIDS defining condition. A decrease in CD4+ T-cells (less than 200 cells/ uL) has been observed to be associated with intestinal parasitic infections, such as *Cryptosporidium, I. belliand and S. Stercoralis*), and with a higher incidence of diarrhoea.[4]

Th17 cell loss and impairment of mucosal integrity

HIV mediated loss of Th17 cells from the gut-associated lymphoid tissue (GALT) has been observed to impair mucosal integrity, and innate defence mechanisms against gut microbes. Th17 cells are important for intestinal homeostasis. Th17 cells are involved in epithelial regeneration, and stimulate the production of defensins and mucin, as well as induce the expression of claudins, which are components of epithelial tight junctions. The Th17 cytokine, interleukin-22 (IL-22) increases the production of the lipopolysaccharide binding protein (LBP) in the liver. Considering, the massive CD4+ T-cell depletion in the lamina propria after HIV infection, it is probable that Th17 cells are also depleted by HIV. Since Th17 cells have multiple roles in controlling epithelial integrity and microbial invasion, the depletion of Th17 is likely to affect the integrity of the GIT.[5] To date, Salmonella has been directly shown to translocate across the GIT barrier, when Th17 cell function is compromised in the GALT, in PLWH.[5]

Impact of HIV infection on lactose absorptive capacity

It has been reported that lactose malabsorption is significantly higher (70%) in PLWH, than HIV-uninfected controls (34%). Furthermore, the degree of lactose malabsorption was found to be significantly greater in PLWH with advanced disease, versus those in the earlier stages of disease. The degree of lactose malabsorption was also related to whether PLWH were symptomatic and had intestinal manifestations, than asymptomatic PLWH and non-HIV infected controls. It is presumed that apart from the presence of the HIV, other factors (probably both structural and immune) determine the enterokinetic alterations responsible for lactase deficiency and lactose malabsorption.[7]

Clinical presentation of enteropathy

A high percentage of PLWH worldwide have been reported to initially present with, or develop, diarrhoea, irrespective of whether they are on HAART or not. In the United States, 50% of PLWH have presented with diarrhoea. However, in developing countries a prevalence of as many as 80% of PLWH have presented with diarrhoea. The presentation of diarrhoea may or may not be in the presence of an opportunistic infection of the GIT. The opportunistic infections that affect the GIT in PLWH include parasitic infections (for example: *Cryptosporidia, Isopora and Cyclospora*), viral [in particular Cytomegalovirus (CMV)], and bacterial [for example: Mycobacterium tuberculosis (TB), Salmonella, Shigella, Campylobacter jejuni and Mycobacterium avium complex (MAC)]. Prompt treatment of CMV is very important, as it is associated with a poor prognosis in PLWH and a high rate of recurrence. A person with GIT MAC usually has disseminated disease, a very low CD4+ T-cell count, and limited survival time. Since the introduction of HAART, the incidence and prevalence of MAC has decreased. TB of the GIT may affect immune-compromised and immune-competent individuals. It is estimated that GIT TB accounts for 1 to 3% of TB cases worldwide. It is commonly found in the region of the ileocaecal valve, but can occur at any region throughout the GIT.[6]

Clinical presentation of HIV-associated diarrhoea varies among PLWH depending on the principal section of the GIT that is involved. Small bowel diarrhoea tends to result in large bulky postprandial stools almost immediately after eating, and the individual may experience postprandial paraumbilical abdominal pain. However, if the affected individual fasts, the diarrhoea significantly decreases. Individuals with small bowel diarrhoea usually experience weight loss. Whilst individuals with large intestine diarrhoea (termed “colitic diarrhoea”) usually present with frequent, small-volume stools, and the stools may have visible blood and mucus. These individuals will usually experience lower-quadrant abdominal pain, and the sensation of rectal urgency. However, in many instances, it may be difficult to differentiate between small- and large bowel diarrhoea.[6]

Opportunistic infections are not limited to the small- and large bowel, and may occur in the upper GIT, including oesophageal pathology (for example: candida oesphagitis, CMV, and herpes simplex virus), and gastric and duodenal pathology (for example: CMV, *Helicobacter pylori* and cryptosporidium). These infections may lead to dysphagia

and hence poor nutritional intake but also recurrent dehydrating vomiting.[8]

Most of the GIT opportunistic infections described will result in further aggravation of HIV-associated enteropathy, due to structural damage and/or immune sensitisation; hence making it difficult to differentiate whether the severity of GIT related symptoms is due to HIV disease progression or the severity of other opportunistic infections.

In a recently published study, Densupsoontorn et al (2009)[9] reported that HIV-infected children with a higher severity of malnutrition and more advanced stages of HIV clinical symptoms, had accelerated whole gastrointestinal transit time. The authors recommended early nutritional intervention for children with severe malnutrition and advanced HIV disease with specialised lactose-free feeds of low osmolality to aid in delaying gastric GIT transit time and to allow for greater nutrient absorption.

The role of gut in HIV disease progression

Immune activation in chronic HIV infection includes polyclonal B cell activation, increased turnover of T-cells, a high frequency of "activated" phenotype T-cells as well as increased levels of cytokines and other proinflammatory mediators. This activation results in the restoration of $CD4^+$ T-cells and immunocompetence but the negative effects include lymph node fibrosis, thymic dysfunction, clonal exhaustion, drainage of memory T-cell pools and generation of more targets for HIV replication.[3]

It has been speculated that due to the massive depletion of memory T-cells in the gut, as well as structural defects of the GIT lining, microbial translocation from the gut is probably involved in driving immune activation. It is thought that the gut-derived microbes or microbial products translocate to the systemic circulation in the absence of overt bacteremia.[3]

Quantification of microbial translocation

Microbial translocation can be quantified by measuring plasma levels of lipopolysaccharide (LPS), the endoxin produced by bacteria that have translocated across the GIT lining. PLWH with acute HIV infection were found to have LPS levels similar to those of non-HIV infected individuals. However, in PLWH with chronic HIV infection, the LPS levels were significantly higher. In an earlier study, non-infected HIV individuals were injected with LPS produced systemic immune activation with increased levels of inflammatory cytokines [for example, tumour necrosis factor, interleukin (IL)-1 receptor antagonist, IL6 and IL8] with plasma LPS levels as low as 14 pg/ml. In studies on PLWH with chronic infection, the LPS levels were found to be 75 pg/ml; hence sufficient to stimulate systemic immune activation.[3]

It is well known that immune activation can be attenuated with potent antiviral therapy (ART), although the decline is much slower than HIV RNA levels and may remain elevated for a year after ART. It has been observed that statistically significant decreases in LPS levels only occur in PLWH after 48 weeks on ART. It is thus appears that ART is currently the most effective way to protect the gut, and help reduce bacterial translocation, and hence reduce chronic systemic immune activation.[3]

Further evidence of the link between bacterial translocation and HIV pathogenesis was recently reported, in which PLWH who had HIV-associated dementia were found to have higher plasma LPS levels when compared with PLWH without neurocognitive impairment. It has been proposed that LPS-mediated monocyte activation and trafficking to the brain may well be the underlying mechanisms of the association between LPS plasma levels (bacterial translocation) and HIV-associated dementia.[5] Recently published research findings also suggest that microbial translocation may be a fundamental mechanism by which the progression of hepatitis C-related liver disease may be accelerated to cirrhosis in PLWH.[10]

HAART and the gastrointestinal tract

Currently, ART has, in most cases, been found to reduce plasma viral loads to undetectable levels resulting in subsequent increases in peripheral blood $CD4^+$ T-cells. Early studies of HIV-associated enteropathy after the initiation of ART documented significant decreases in GIT symptoms, namely, abdominal bloating, cramping and loose stools. However, a decrease in viral replication and $CD4^+$ T-cell reconstitution does not occur at a similar rate at all anatomic sites, especially in the GIT. Recent studies have shown that in the small bowel $CD4^+$ T-cell reconstitution was poor, and in PLWH with acute HIV infection who had been on highly active antiviral therapy (HAART) had a much greater reconstitution (twofold) of $CD4^+$ T-cells when compared with individuals with chronic HIV infection (the latter individuals rarely ever reconstituted GIT $CD4^+$ T-cells to normal levels). Importantly, it was also observed that although many PLWH treated with HAART reconstituted peripheral $CD4^+$ T-cells, no HIV-infected individual ever reconstituted GIT $CD4^+$ T-cells to levels observed in non-infected individuals.[2]

GIT $CD4^+$ T-cells have been observed to still produce HIV virus, even years after the initiation of HAART. Although the GIT is well vascularised and ART drugs should be bioavailable, high levels of multidrug-resistant proteins, also named "toxin pumps" (such as P-glycoprotein), are expressed on the apical surface of columnar epithelial cells of both the small and large intestine. It is speculated that these multidrug-resistant proteins, have specificity for protease inhibitors and nucleoside analogs and may reduce the local concentration of ART drugs to infected cells in the GIT, thus allowing the virus to slowly replicate and limit reconstitution of $CD4^+$ T-cells.[2]

Ongoing local inflammation in the GIT maybe a second reason for the failure of PLWH on HAART to reconstitute $CD4^+$ T-cells. Local immune activation has been shown to be associated with fibrosis of the lymphoid architecture in peripheral lymph nodes, which in turn influences the degree of peripheral blood $CD4^+$ T-cell

reconstitution following the initiation of HAART. Recent findings also suggest that the fibrotic deposition of collagen also occurs in the GIT Peyer's patches, even during the acute phase of HIV infection. The degree of architectural damage of the Peyer's patches predicts GIT CD4+ T-cell depletion after HAART. Although HAART reduces GIT immune activation, it is thought that the ability of the remaining (but damaged) lymphoid to support significant CD4+ T-cell reconstitution is permanently damaged.[2] As many as 30% of PLWH on HAART, fail to reconstitute CD4+ T-cells, despite HIV-viremia control, and are described as immunologically-nonresponders (INRs). INRs have an increased risk of HIV/ AIDS progression.[11]

Plasma citrulline: A biomarker of enterocyte mass in PLWH?

Plasma or serum citrulline assays have recently emerged as being the best tool in assessing enterocyte mass, irrespective of the aetiology of the intestinal mucosal disease. Citrulline is the metabolic product of glutamine, and its related amino acids, and arginine, and is specifically synthesised by small bowel enterocytes. Citrulline has been validated for quantitative enterocyte assessment in villous atrophy disease. Citrulline plasma levels are not influenced by nutritional status, level of hypoalbuminaemia, or inflammatory status. The only limitation in interpreting plasma levels is the presence of significant renal failure (creatinine clearance of < 30 ml/min) because citrulline is metabolised into arginine in the proximal convoluted tubules in the kidneys. A recent study[12] reported that plasma citrulline assays were a reliable indicator of severe chronic infectious enteropathy in PLWH, and hence a reliable predictor of the need for parenteral nutrition (PN) for such cases. A low citrulline level of < 10 umol/L is considered an indication for PN, whereas for an individual with a citrulline level of > 10 umol/L, enteral route nutritional support is recommended. Citrulline is easy to measure through ion-exchange or reverse-phase liquid chromatography, which could be performed in better equipped hospital laboratories.[12]

The role of HIV vaccines in enhancing GIT mucosal cell immunity

There is some promising evidence which suggests that direct surgical introduction of a vaccine, (replication-competent recombinant adenovirus {rAd} vectors, specifically rAd5), rather than oral gavage, resulted in 100-fold higher transgene expression, and which stimulated potent CD8+ T-cell responses in the intestinal and systemic compartments. These responses could be further enhanced through intramuscular rAd5 injections.[13] The activation status of CD8+ T-cells is considered to be one of the best predictors of HIV disease progression.[5]

Conclusion

In conclusion, the better understanding of the pathophysiology of HIV enteropathy has contributed to the better management of diarrhoea in PLWH. Further research is likely to yield other therapeutic approaches which will further facilitate the management of diarrhoea and contribute to further improvements in the quality of life of PLWH.

References:

1. Lackner AA, Mohan M, Veazey RS. The Gastrointestinal Tract and AIDS Pathogenesis. Gastroenterology 2009;136:1966–78.
2. Brenchley JM, Douek DC. HIV infection and gastrointestinal immune system. Mucosal Immunology 2008;1 (1):23–30.
3. Douek D. HIV Disease Progression: Immune Activation, Microbes and a Leaky Gut. International AIDS Society – USA 2007;15 (4):114–7.
4. Assefa S, et al. Intestinal parasitic infections in relation to HIV/ AIDS status, diarrhea and CD4 T-cell count. BMC Infectious Diseases 2009;9:155.
5. Hofer U, Speck RF. Disturbance of the gut-associated lymphoid tissue is associated with disease progression in chronic HIV infection. Semin Immunopathol 2009;31:257–66.
6. Cello JP, Day LW. Idiopathic AIDS Enteropathy and Treatment of Gastrointestinal Opportunistic Pathogens. Gastroenterology 2009;136(6):1952–65.
7. Corrazza GR, et al. The impact of HIV infection on lactose absorptive capacity. J Infect 1997;35(1):31–35.
8. Cooke ML, et al. Endoscopy Findings in HIV-Infected Children from Sub-Saharan Africa. Journal of Tropical Pediatrics 2009;55(4):238–43.
9. Densupsoontorn N, et al. Whole Gastrointestinal Transit Time is Associated with Clinical Severity and Nutritional Status of HIV-Infected Children. J Med Assoc Thai 2009;92(7):914–9.
10. Balagopal A, et al. Human Immunodeficiency Virus-Related Microbial Translocation and Progression of Hepatitis C. Gastroenterology 2008;135:226–33.
11. Marchetti G, et al. Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. AIDS 2008;22:2035–8.
12. Crenn P, et al. Plasma citrulline is a biomarker of enterocyte mass and an indicator of parenteral nutrition in HIV-infected patients. Am J Clin Nutr 2009;90:587–94.
13. Wang L, et al. Delivery of Human Immunodeficiency Virus Vaccine Vectors to the Intestines Induces Enhanced Mucosal Cellular Immunity. Journal of Virology 2009;83(14):7166–75.

The ethical approach to evidence-based medicine

Kruger M
Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa
Correspondence to: Dr Mariana Kruger, e-mail: marianakruger@sun.ac.za OR aec1@sun.ac.za

Abstract

This paper will explore the role of evidence-based medicine in ethical practice of health care professionals. It will also address some of its limitations and potential for negative impact on health care.

S Afr J Clin Nutr 2010;23(1) Supplement:S69-S70

Evidence-based medicine has had a major impact on health care in the last 30 years. This approach has lead to the critical appraisal of therapeutic knowledge. Archie Cochrane, an epidemiologist, gave a series of lectures in 1972 regarding his reflections on the effectiveness and efficiency of health services.[1] He introduced the scientific and practical evaluation of treatment modalities and drew attention to the possible harm and even iatrogenic injury, as well as waste, that can occur if systematic review of interventions is not done.

The concept of evidence-based medicine is defined as "the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions".[2] The practice of evidence-based medicine implies the use of individual clinical expertise, in combination with a systematic review of the best available clinical evidence, which is derived from the relevant research.[2] The aim is to use the most efficacious interventions in the pursuit of quality and quantity of life. This approach is especially useful in medical education to teach best clinical practice.

Evidence-based medicine relies on a hierarchy of evidence, which is ranked from absolute proven interventions to the least reliable knowledge.[3] The process of examining evidence involves multiple steps, where the first involves using the available information to formulate answerable questions.[4] The next step is to search for the evidence that can best answer these questions. The third step involves the evaluation of the evidence for its importance and validity. The clinician thereafter has to integrate these findings with her/his clinical expertise and apply it in clinical practice in combination with patient values. Continuous evaluation of clinical practice is the last ongoing step. There are at present several evidence-based resources to assist health care professionals, which provide peer reviewed critical appraisal of the best evidence for intervention or treatment, of which the Cochrane database is probably the best known.

The practice of evidence-based medicine usually assists in answering two questions, namely what is in the best interest of the patient and how should we allocate of health care resources fairly.[5] Evidence-based medicine enables the health care practitioner to strive for a clinical ideal, which addresses our ethical responsibility towards the best interest of our patient. For this purpose health care professionals should pursue health.[5] This should be done through the pursuit of the most effective ways of achieving health, which is a generally acceptable value shared by most people. As professionals it is through the pursuit of truth, that we will find most effective means to health.[5] The premise is in general valid, and most health care professionals and researchers will be in agreement with this premise. A second premise is that if we pursue evidence-based medicine, we shall increase the likelihood of finding truth, which shall ensure the provision of the effective means to achieve health.[5] This is not necessarily valid, since the assumptions are that there is no bias and that inferences made are not influenced by subjective interpretation.

This necessitates an investigation into the potential limitations of evidence-based medicine. The first is that there may be the potential for bias.[5] Funding of health care research is conducted where there is commercial value involved for the intervention tested and can in this way create bias towards research that will generate good return on investment. Furthermore, there can be a technical bias, since we may conduct only research where we know how to do it, leaving other fields of health care with inadequate or no research. Another potential bias is a publication bias, since only positive results are published, leaving huge gaps in knowledge regarding interventions that did not whave a positive effect on health or, indeed, did harm.

Evidence-based medicine is, furthermore, better suited to secondary and tertiary health care, since it deals with a single disease with well-defined symptoms and clinical signs. However, in primary health care it is not always that easy, since the symptoms are

often non-specific, are still evolving and may be related to complex psychosocial problems.[6] Evidence-based medicine is also not very helpful in, especially, rare diseases. At the same time, evidence may also be supported poorly by relevant research, since studies may contradict each other or may be inconclusive. The application of the evidence may also be problematic due to the individual patient with confounding health care problems or due to patient value systems.

The gold standard for evidence-based clinical information is the randomised controlled trial (RCT), which is a valuable approach to limit the use of worthless treatments and promote effective treatments.[6,7] Unfortunately RCT is limited to only a section of health care management, where interventions are involved in a single entity under investigation, leaving other health care sections not being examined.[6,7] Furthermore, there should be genuine "therapeutic equipoise" which implies that the there is a valid doubt about the value of the treatment modalities under investigation, which can only be answered by the RCT. Again this is difficult to achieve when there is great benefit to be obtained if an intervention will have great commercial value. Another important factor is that RCT only produces the average effect, while some patients may experience harm crudely applied. RCT can therefore generate valuable evidence for efficacy in the context of a single disease with measurement between interventions, but there is a paucity of RCT in primary care and other fields of health care.[6] This is especially true also for rare disease where it is not possible to conduct RCT or where other ethical issues are involved, such as lack of informed consent as illustrated by GSSI-2 trial, which is widely quoted as evidence due to its outcome.[8,9]

As already referred to above, the information generated by the RCT does not take into account non-quantifiable factors and does not provide a framework to integrate such knowledge, such as differences in social and cultural backgrounds that may impact on health.[6,7] RCT also relies on the classical theories of statistical inference, requiring large sets of data.[7] An important argument regarding the use of statistical inference is whether this truly provides measures of objective probability versus rational subjective interpretation.

Another limitation of evidence-based medicine relying on RCT is that new skills and interventions, which should be developed to ensure that there is continuous health care improvement, may be difficult to initiate. These very necessary novel interventions will initially not be supported by evidence and a good example is pain management in neonatology. Pain management per se is difficult to assess, and even more so in newborn babies. At the same time the majority of therapies are being used off label for these infants, and therefore there is no evidence to be derived from the appropriate RCT. This leads to the situation that there is little active research into this field, which is potentially harmful to neonates. We can conclude that there are competing claims that cannot all be resolved by evidence-based medicine, i.e. relying on RCT for the evidence.

Another important negative impact of evidence-based medicine is that it may create a barrier to quality health care in the context of high demand versus scarce resources. The different stakeholders may interpret the evidence differently and their conclusions will not be congruent with each other.[10] Problematic values in this context are justice and quality of life, which are often replaced by more easily measured values such as cost and mortality respectively. Resource allocation on the basis of evidence-based medicine involves value judgements and often a lack of evidence means a lack of value.[10] Government and service providers may use evidence-based medicine to the disadvantage of patients when they agree to only fund what has been proven by evidence-based medicine, which usually implies RCT. This again implies that only conditions that are well researched will get access to resources, while other areas where there is little or no evidence, will receive no resource allocation.[10] If evidence-based medicine is used for "evidence-based purchasing", it will create a tension between the best interest of the individual versus the population .[10]

A further problem with evidence-based medicine is that it is doctor-driven and patients have little influence on the subject matter. Another concern is that it only focuses on the evidence for efficacy and not on the way the information was obtained. Again the GISSI-2 trial is often quoted for proof of efficacy, while the study did not obtain informed consent from participants and therefore was conducted not respecting patient autonomy.[8]

In conclusion evidence-based medicine is probably a simplistic solution to inherent complex problems. However, even if there are limitations, it is a shared value in the sense that we all want to be treated with the best proven intervention and therefore we do expect health care professionals to practice their profession by combining their individual clinical skill with evidence-based medicine.

References

1. Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospitals Trust, 1972.
2. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–72.
3. Gupta M. A critical appraisal of evidence-based medicine: some ethical considerations. J Eval Clin Pract 2003;9:111–121.
4. Straus S, McAlister FA. Evidence-based medicine: a commentary on common criticisms. CMAJ 2000;163:837–841.
5. Culpepper L, Gilbert TT. Evidence and ethics. Lancet 1999;353:829–831.
6. Slowther A, Ford S, Schofield T. Ethics of evidence based medicine in the primary care setting. J Med Ethics 2004;30:151–155.
7. Ashcroft RE. Current epistemological problems in evidence based medicine. J Med Ethics 2004;30:131–135.
8. Gruppo Italiano per lo Studio della Sopravvivenza nell Infarto Miocardio. GSSI-2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet 1990336:65–71.
9. Rogers WA. Evidence-based medicine and justice: a framework for looking at the impact of EBM upon vulnerable or disadvantaged groups. J Med Ethics 2004;30: 141–145.
10. Saarni SI, Gylling HA. Evidence-based medicine guidelines: a solution to rationing or politics disguised as science? J Med Ethics 2004;30:171–175.

Agreement between NRS-2002 and MUST nutrition risk scores – a retrospective study

[a] **Dannhauser A,** PhD [b] **Nel M,** MMedSc
[a] Department of Nutrition and Dietetics, School of Allied Health Professions, Faculty of Health Sciences, University of the Free State, Bloemfontein
[b] Department of Biostatistics, Faculty of Health Sciences, University of the Free State, Bloemfontein
Correspondence to: Dr André Dannhauser, e-mail: DannhauserA@ufs.ac.za

Introduction

The nutritional status of hospitalised patients has been a growing concern during the past four decades. Worldwide studies indicate that 30% to 60% of hospitalised patients are malnourished.[1] The complications of undernutrition, which include prolonged healing, increased length of hospital stay and increased hospital cost are well known. Early identification of undernutrition and/or risk to develop undernutrition while in hospital has been recommended.[2] Various nutrition risk screening tools have been developed and are frequently used in the nutritional management of hospitalised patients. Based on sensitivity and specificity, the following four screening tools seemed to be valid and therefore recommended for nutrition risk screening: the Nutrition Risk Screening tool (NRS-2002), the quick and easy Malnutrition Universal Screening Tool (MUST), the Malnutrition Screening Tool (MST) as well as the Short Nutritional Assessment Questionnaire (SNAQ).[3]

Since 2003, the Nutrition Risk Screening tool (NRS-2002), developed by European Society for Clinical Nutrition and Metabolism (ESPEN)[2] has been used to determine the nutritional risk of patients admitted to Pelonomi, Universitas and National Hospitals in Bloemfontein. Forty to 60% of these patients had a high nutritional risk and would likely benefit from nutritional support.[4] However, the need for a more easy to apply screening tool was identified. The MUST was considered quick and easy and the screening criteria were available on the NRS screening form.

In view of the paucity of comparative data in the country on the use of such screening tools, we compared, in this study, the results obtained from MUST and NRS-2002 screening tools in the 2005–2008 period with the aim of establishing which of the two tools would be the most appropriate to use in the Bloemfontein academic hospitals.

Methods

The study was based on the screening results of a sample of adult patients (N = 3938) aged 18 years and older, who were admitted during February to October 2005–2008 to the medical and surgical wards in Pelonomi and Universitas Hospitals and the cancer wards of the National Hospital. Ethics approval was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State (ETOVS number 30/01).

Final year dietetic students were trained to complete the adapted NRS-2002[2] questionnaire and to take the anthropometric measurements. For standardisation purposes, pilot studies, using the final year students of the respective years over which the study was conducted, were implemented in January of each year. Anthropometric techniques, as described by Lee and Nieman[5] were used to determine current weight, height, knee-height and mid-upper arm circumference. In patients from whom standing height and weight could not be obtained, equations for estimating stature from knee-height and equations to estimate body weight from knee-height and mid-arm circumference[5] were used. Reported pre-illness weight was also noted. All new admissions were screened on weekdays only.

Statistical analysis

A non parametric Bland-Altman analysis was used to assess the level of agreement between the two methods,[6] where the 2.5th percentage and 97.5th percentage were calculated as the limits. The risk categories for BMI, weight loss and appetite loss used for MUST[2] were applied on the screening results of 2005–2008 and the final score was calculated and described by means of sensitivity and specificity, for which 95% confidence intervals for the percentage were calculated.

Results

The limits of agreement between the scores obtained by the NRS-2002 and the MUST ranged from -1 to 5 (Figure 1a). The two methods did not consistently provide similar scores because there was a level of disagreement that included clinically important discrepancies of up to a score of 6.

How small the limits of agreement should be to conclude that the methods agree is a clinical, not a statistical decision. Thus to find a stricter cut-off range, the limits of agreement were narrowed and determined by a clinical decision of $\pm$ 1, which showed an even larger level of disagreement (Figure 1b).

The diagnostic accuracy of the two methods was calculated from a 2x2 Table. The outcome of the risk obtained from the MUST was measured against the risk outcome obtained from the NRS-2002. The positive predicted value of the MUST as measured against the

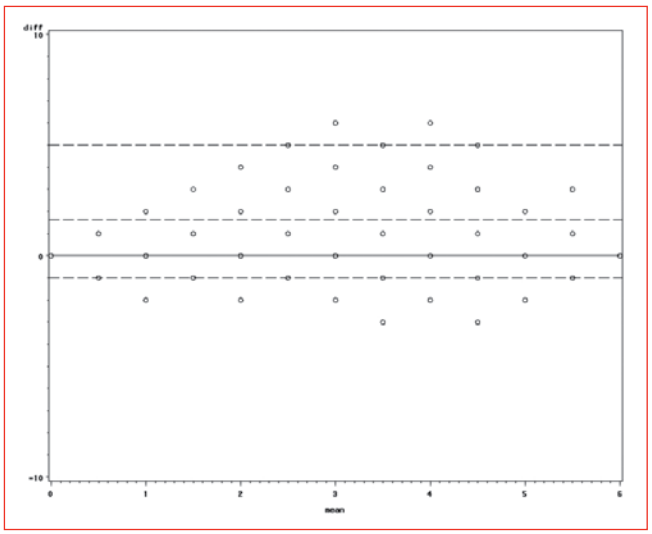


Figure 1a: BlandAltman -1 and 5 cut-off values

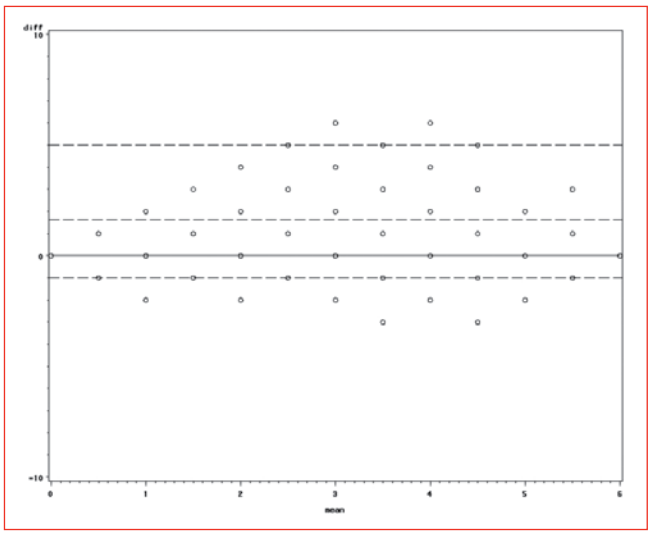


Figure 1b: BlandAltman -1 and 1 cut-off values

Figure 1: Bland-Altman analysis depicting the level of agreement between the Nutrition Risk Score/indication of nutritional risk that needs intervention by a dietitian using the risk scores obtained by the two methods. The Bland-Altman analysis involves the plotting of the difference between the measurements of the same parameter obtained with two different techniques against the mean of the two techniques. Points showing perfect agreement will lie on the horizontal line drawn through the value 0. The further away the points lie from this line, the worse the level of agreement.[6]

NRS-2002 was 89.5%, while the negative predictive value was 61.2%. The sensitivity was 59.1% with 95% CI [57.1% ; 61.1%] and the specificity was 90.3% with 95% CI [88.9% ; 91.7%].

Discussion

The diagnostic accuracy of any screening tool is important as it determines whether a patient will be accurately diagnosed as nutritionally at risk and would need nutrition support. The positive predictive value of the MUST was high (89.5%) while the negative predictive value was low (61.2%). The positive result is very predictive because there is 89.5% certainty that a person with a positive result based on the test will be identified.

The sensitivity of the MUST was low (59.1%), and the specificity was high (90.3%). If the sensitivity and specificity of 70% that was used by Neelemaat et al[3] to represent validity is used as the criterion, then the sensitivity of the MUST compared to the NRS-2002 was too low.

The limits of agreement by the Bland-Altman analysis showed a large level of disagreement between the two methods. Narrowing the limits of agreement would contribute to a more accurate assessment of the patient who would need nutritional support, thus a clinical decision of ± 1 was used, which shows how large the level of disagreement really is.

Conclusion

Findings obtained by the MUST screening tool were not found to be in agreement with those of the NRS-2002. The fact that the MUST was derived from the NRS-2002 and was not determined on its own probably contributed to the disagreement found between the two methods. It is recommended that the NRS-2002 be compared prospectively with the MUST and other screening tools.

References

1. Kubrak C, Jensen L. Malnutrition in acute care patients: A narrative review. International Journal of Nursing Studies 2007;44:1036–1054.
2. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for Nutrition Screening 2002. Clinical Nutrition 2003;22(4):415–421.
3. Neelemaat F, Kruizenga HM, Van Ballegooijen H, Bokhorst-de van der Scheren MAE. Diagnostic accuracy of NRS-2002, MST, MUST and SNAQ in the same adult population. Clinical Nutrition. Abstracts of the 29th Congress of ESPEN 2007;2 (Supplement 2): S10. (Abstract)
4. Dannhauser A, Jonker E, Nel M. Nutrition Risk Screening in hospital patients. Astra Zenica Faculty Forum of the Faculty of Health Sciences, University of the Free State 2007:9. (Abstract)
5. Lee RD, Nieman DC. Nutritional Assessment. Boston: McGrawHill 2003:216–238.
6. Bland JM, Altman DG. Applying the right statistics: analysis of measurement studies. Ultrasound Obstet Gynecol 2003;22:85–93.

Agreement between estimated and measured heights and weights in hospitalised patients – a restrospective study

[a] **Van den Berg L,** PhD [a] **Dannhauser A,** PhD [b] **Nel M,** MMedSc
[a] Department of Nutrition and Dietetics, School of Allied Health Professions, Faculty of Health Sciences, University of the Free State, Bloemfontein
[b] Department of Biostatistics, Faculty of Health Sciences, University of the Free State, Bloemfontein
Correspondence to: Dr Louise van den Bergm e-mail: vdBergVL@ufs.ac.za

Introduction

The European Society for Clinical Nutrition and Metabolism (ESPEN) estimates that about 30% of all hospital patients are undernourished and need special nutritional care. ESPEN advises that all patients be screened for nutritional risk on admission. An ideal nutritional risk screening tool should be simple and quick to use by nursing staff when admitting patients to hospital. Tools recommended by ESPEN are the NRS 2002, MUST and MNA – all of which utilise body mass index (BMI = kg/m^2) and require accurate recording of a patient's height and weight.[1]

In reality, however, patients often cannot stand up straight for accurate height measurement, or are unable to step on a scale. In such cases, height and weight values are often obtained from the patient or their relatives, who either do not know, or do not report the values accurately, particularly in the South African setting where many patients do not own a scale and language barriers complicate communication. In many institutions the height and weight recorded in the patient's file on admission, are also values "guessed" by the attending nurse.

Various indirect methods have been developed to estimate height and weight. Height may be estimated using knee height (KH), and weight using KH and mid upper-arm circumference (MUAC).[2] These methods have been tested and validated in various population groups in studies where reliability was carefully controlled. In the academic hospitals in Bloemfontein, South Africa, dietetic interns (final year students performing an internship) routinely screen newly admitted patients using the NRS2002. Since 2003, certain wards in the three academic hospitals have been identified for nutritional screening as part of an ongoing research study. Since 2005 the students have been recording both measured and estimated heights and weights (using the above-mentioned methods), where possible. The study reported here aimed to assess the level of agreement between the measured and estimated heights and weights of patients as recorded by the dietetic students, in order to determine whether including these indirect methods in a nutritional risk screening tool would deliver reliable results in cases where direct height and weight measurements were not possible.

Methods

This study was based on the screening records (recorded by dietetic interns using the NRS 2000) of patients (≥ 18 years) admitted to the medical and surgical wards in Pelonomi and Universitas Hospitals and the cancer wards of National Hospital from 2005 to 2008. The students were trained on various occasions during their studies and again just prior to starting with the screening, in standardised techniques to measure KH and MUAC. In 3732 patients height was both measured, and estimated using a standardised method based on KH. In 3774 patients weight was both measured, and estimated using a standardised method based on KH and MUAC. BMI was calculated based on measured and estimated heights (N = 3642) and weights (N = 3663) respectively. Bland-Altman analysis was used to assess the levels of agreement between the estimated and measured values.[3]

Results

The Bland-Altman plots indicated that the 95% limits of agreement between measured and estimated heights ranged from -8 cm to +33 cm, with a median of 5 cm (Figure 1a). The 95% limits of agreement between the measured and estimated weights ranged from -16 kg to 44 kg, with a median of 5 kg (Figure 1b).

The 95% level of agreement between BMI based on measured height and BMI based on estimated height ranged from -14.6 kg/m^2 to +2.5 kg/m^2, with a median of -1.5 kg/m^2 (Figure 1c). The 95% level of agreement between BMI based on measured weight and BMI based on estimated weight ranged from -5.8 kg/m^2 to +17.1 kg/m^2, with a median of 1.8 kg/m^2 (Figure 1d). Thus the methods do not consistently provide similar results.

Discussion

Most nutritional screening tools rely on BMI and require accurate weight and height measurements. In the hospital setting these measurements are sometimes difficult to perform and often need to be estimated. Standardised estimation equations are available and in this study height was estimated using KH, and weight was estimated using KH and MUAC, during nutritional risk screening performed by dietetic interns. The results show wide disagreement between the actual measured heights and weights and those estimated using the standardised estimation techniques. Using these estimations in BMI calculations predictably led to a high level of disagreement with BMI-values obtained from actual measured heights and weights. These estimation methods therefore, although validated in studies where reliability was carefully controlled, when applied in routine practice, delivered clinically important discrepancies.

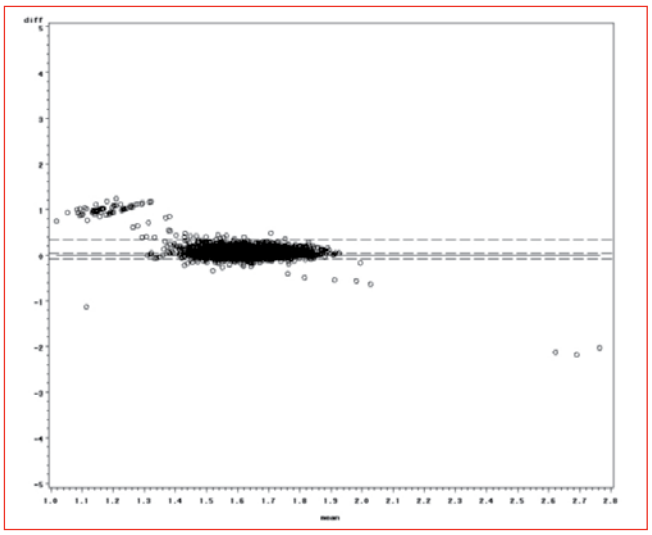


Figure 1a

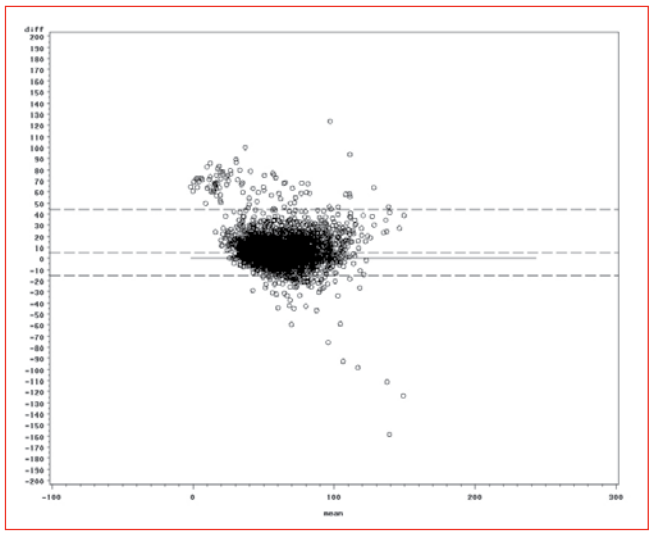


Figure 1b

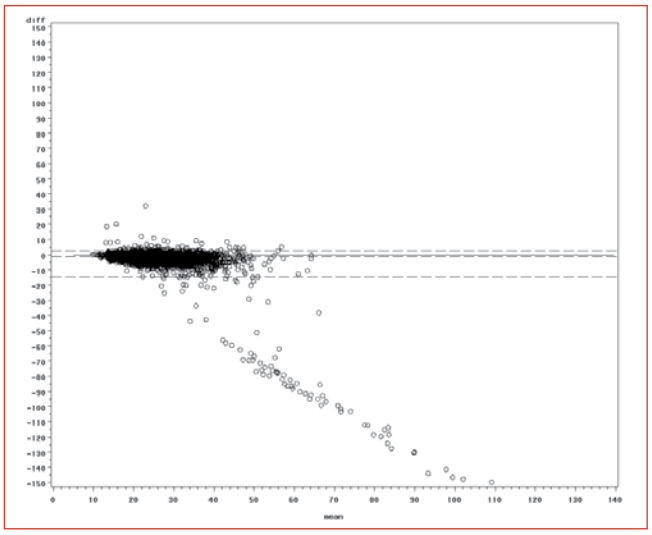


Figure 1c

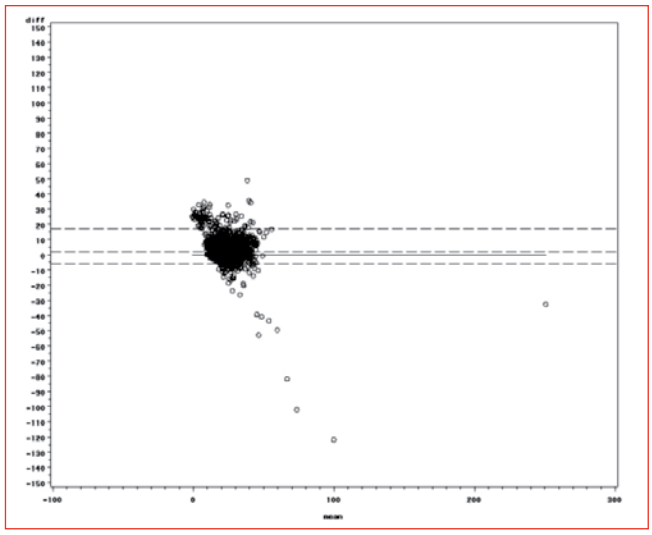


Figure 1d

Figure 1: Bland-Altman plots depicting the levels of agreement between (a) measured height and height estimated with Knee Height (KH), (b) measured weight and weight estimated with KH and Mid Upper-Arm Circumference (MUAC), (c) Body Mass Index (BMI) calculated using measured height and BMI calculated using estimated height, and (d) BMI calculated using measured weight and BMI calculated using estimated weight. Bland-Altman analysis involves the plotting of the difference between measurements of the same parameter obtained with two different techniques against the mean of these measurements. Points showing perfect agreement will lie on the horizontal line drawn through the value 0. The further away the points fall from this line, the worse the level of agreement.[3]

Conclusions

A nutrition screening tool must be simple and quick to perform, but the accuracy of the assessment results will determine whether the patient will be referred for appropriate nutritional intervention or not. The results of this study emphasise that techniques making use of KH and MUAC to estimate height and weight may be too complicated to be routinely applied with acceptable reliability by students. For busy nursing staff it may only be worse. Sufficient training of staff in these techniques would be very important. Furthermore, staff would need frequent reminder of the correct way to perform the technique – for example visual aids such as posters, videos or video clips that can be run on a computer in the ward could be made available to staff. Alternatively other indirect measures such as ulnar length or demispan[4] may be used for height estimations. Whether these would give more reliable results in the routine setting, remains to be determined.

References

1. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN Guidelines for nutrition screening 2002. Clinical Nutrition 2003;22:415–421.
2. Lee, R.D and Nieman, D.C. Nutritional Assessment. 2003. Third Edition, Mc Graw Hill Company: New York: 221, 227.
3. Bland KM, Altman DG. Applying the right statistics: analysis of measurement studies. Ultrasound Obstet Gynecol 2003;22:85–93.
4. Thomas B, Brioni J. Bristish Dietetic Associations's Manual of Dietetic Practice. 2007, Blackwell Publishing Ltd, Oxford, UK: 62, 379.

The relationship between serum protein and mortality in adults on long-term haemodialysis. A meta-analysis

Herselman M, PhD **Esau N,** BSc Dietetics **Kruger J-M,** MNutr
Labadarios D, MBChB, PhD, FACN **Moosa MR,** MD
Division of Human Nutrition, Stellenbosch University and Tygerberg Academic Hospital

The aim of this systematic review was to explore the relationship between serum protein and all-cause and cardiovascular mortality in adult patients on maintenance haemodialysis. We searched the Medline, Science Citation Index, Academic Search Premier, Cochrane Library and Embase electronic data bases. Data extraction and quality assessment were done independently by two reviewers and results were pooled using the random effects model. Cochran's Q was used to identify heterogeneity and a funnel plot was used for assessment of publication bias. A meta-analysis was performed on 38 studies reporting on serum proteins, inflammatory markers and mortality. A significant inverse relationship was found between serum albumin and all-cause [HR 0.7038 (CI 0.6367 to 0.7781)] and cardiovascular mortality [HR 0.8726 (CI 0.7909 to 0.9628)], with a significantly stronger relationship with all-cause mortality ($p = 0.0014$). Pooled results for C-reactive protein showed a weak but significant direct relationship with all-cause mortality (HR 1.0322; 95%CI 1.0151 to 1.0496) but not with cardiovascular mortality (HR 1.0172; 95%CI 0.9726 to 1.0639). A high degree of heterogeneity was identified between studies and an asymmetrical funnel plot for serum albumin is suggestive of publication bias. From the meta-analysis, it is concluded that serum albumin showed a significant inverse relationship with both all-cause and cardiovascular mortality, with C-reactive protein showing a significant direct relationship with all-cause mortality but not with cardiovascular mortality. The potential adverse effects of malnutrition and infections in relation to mortality highlight the need for continued treatment of infections and correction of malnutrition in dialysis patients.

Relationship between nutritional status and mortality in adults on maintenance haemodialysis. A meta-analysis

Herselman M, PhD **Esau N,** BSc Dietetics **Kruger J-M,** MNutr
Labadarios D, MB ChB, PhD, FACN **Moosa MR,** MD
Division of Human Nutrition, Stellenbosch University and Tygerberg Academic Hospital

The aim of this systematic review was to determine the strength and direction of the association between body mass index (BMI), subjective global assessment (SGA) and mortality in adult patients on maintenance haemodialysis. Electronic data sources included Medline, Science Citation Index, Academic Search Premier, the Cochrane Library and Embase for the period 1963–2008. Data extraction and quality assessment were done by two independent reviewers. During meta-analysis of 12 studies reporting on BMI and four studies reporting on SGA results were pooled using the random effects model. Cochran's Q was used to identify heterogeneity. Higher levels of BMI were associated with a weak but significant reduction in overall mortality (log HR -0.0413, CI -0.0588 to -0.0237) with no significant difference between all-cause and cardiovascular mortality ($p = 0.4197$). The relationship between mortality and SGA was also not significant (log HR 0.0643, CI -0.1713 to 0.2999). A high degree of heterogeneity was found for both BMI and SGA. In conclusion, BMI showed a weak but significant inverse relationship with all-cause and cardiovascular mortality but the meta-analysis failed to confirm a significant relationship between SGA and mortality.

Nutritional management of common opportunistic infections (HIV-context)

Mutemi E
Nutrition consultant, National AIDS and STI control programme (NASCOP), Kenya

The HIV virus attacks the immune system. In the early stages of the infection a person shows no visible signs of illness but later many of the signs of AIDS will become apparent, including weight loss, fever, diarrhoea and opportunistic infections (such as sore throat and tuberculosis).

Good nutritional status is very important from the time a person is infected with HIV. Nutrition education at this early stage gives the person the opportunity to adopt healthy eating habits and to take action to improve food security in the home, particularly as regards the cultivation, storage and cooking of food.

Good nutrition is also vital to help maintain the health and quality of life of the person suffering from AIDS. Infection with HIV adversely impacts on the immune system, which leads to other infections with attendant lower food intake because of reduced appetite and/or impaired nutrient absorption leading to weight loss and malnutrition One of the possible signs of the onset of clinical AIDS is a weight loss of about 6–7 kg for an average adult. When a person is already underweight, a further weight loss can have serious adverse effects on the health and nutritional status of the individual. A healthy and balanced diet, early treatment of infection and proper nutritional recovery after infection can improve quality of life. Additionally, the treatment of opportunistic infections in combination with the therapy for HIV may influence eating patterns and nutritional status.

When nutrient needs are not met, recovery from an illness is known to be prolonged. During this period the family will have the burden of caring for the sick person, paying for health care and absorbing the loss of earnings while the ill person is unable to work. These and other benefits derived from maintaining a good nutritional status in such individuals is therefore of paramount importance.


Nestlé Nutrition Institute Africa