Nutritional support: how much for how much?

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SUMMARY Although malnutrition is associated with poor clinical outcome, it cannot be inferred that better nutrition will improve clinical outcome. Efficacy of a proposed regimen is best established by prospective, randomised, controlled trials. Cost effectiveness is only an issue if efficacy exists. Patients with long term temporary, or permanent, inadequate bowel syndrome are candidates for parenteral nutrition. Most of the prospective, randomised, controlled trials testing the value of nutritional support in other diseases, however, have failed to show that this treatment has a beneficial clinical effect. Areas where these trials have shown a possible clinical benefit include the perioperative care of patients with upper gastrointestinal cancer, elemental diet treatment of Crohn's disease, and branched chain amino acid infusions in hepatic encephalopathy. Even in these instances, it is not clear that such treatment will prove to be cost effective (compared with other currently available treatments).

About 50 years ago Studley observed that patients who had lost more than 20% of their weight had an eight-fold higher surgical mortality compared with those who had lost less.¹ The association between poor nutritional variables and poor clinical outcome has been one of the bases for the growth of therapeutic nutritional support, now a multibillion dollar a year endeavour. Association, however, does not prove causation; a poorer nutritional state may be a consequence of a more severe underlying disease. Therapeutic efficacy is traditionally established by prospective, randomised, controlled trials. This paper will review the prospective randomised controlled trials of nutritional support, identify areas where efficacy is or may be established, and consider the cost of nutritional support in those areas.

All of the reviewed trials measured clinical outcome criteria such as morbidity, mortality, or duration of hospital stay. Studies on nutritional criteria only such as nitrogen balance or serum albumin will not be discussed. In the studies of parenteral nutritional support at least one group received intravenous nitrogen (hydrolysates or amino acids) with or without high calorie loads and a control group did not receive nitrogen parenterally. In the trials of enteral nutritional support an organised effort was made to provide enteral feeding

(usually liquid diets) to one (or more) group(s) but not to the control group. At the time of writing, 64 parenteral and 29 enteral trials have been identified. In the following discussion, unless otherwise indicated, differences in outcome between the study and control groups will only be noted if they are significant ($p < 0.05$).

Cancer

Patients with cancer are often malnourished: chemotherapy or radiation treatment exacerbate this problem. Nutritional support might be expected to benefit this group of patients. Unfortunately, few positive effects of nutritional support in "oncotherapy" have been shown.

The role of parenteral nutrition as an adjunct to treatment has been evaluated in 17 trials.²⁻²² None of these studies has shown any favourable effect of parenteral nutrition on survival; patients with colorectal cancer receiving parenteral nutrition had a significantly worse survival (79 days) compared with that of the control group (308 days).⁴ Haematological variables were favourably influenced in two studies,^{8, 17} but in three other trials^{11, 13, 20} those receiving parenteral nutrition had a poorer outcome. Gastrointestinal side effects were improved in two^{5, 8} but worse in two others.^{4, 20} All seven trials^{5, 6, 11, 13, 15, 16, 20} reporting on the rates of infectious complications found them to be higher in those receiving parenteral nutrition; in four^{5, 13, 15, 20} the

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differences were significant. There was an increased incidence of bleeding in children treated with radiation and parenteral nutrition.¹⁹

Terminal patients receiving only parenteral nutrition – that is, no specific treatment for cancer – lived 46 days, compared with seven days in the control group.¹⁷ This observation has no important clinical application.

Enteral nutrition has also not had an important effect in this area. Only one²³ of five^{23–27} trials evaluating elemental diets had any remotely favourable effect at all, a reduction in diarrhoea in patients undergoing radiation ($0.10 > p > 0.05$). Another four trials found liquid feedings^{28–30} or intact food-stuffs (D Nixon, personal communication) to be of little benefit; in one²⁸ of these trials, there was less neutropenia in those receiving enteral nutrition.

Perioperative nutritional support

Four trials have evaluated the use of the peripheral infusions of amino acids during the perioperative period (J Daly, personal communication).^{31–33} None showed any effect of this treatment on the morbidity or mortality of the surgical patients. Four other trials found that parenteral nutrition did not affect patients undergoing cardiac, otolaryngological, urological, or vascular procedures.^{34–37}

Three studies of parenteral nutrition were directed at patients who had undergone colorectal surgery.^{38–40} Although the perioperative mortality was uninfluenced, in two^{38–40} the duration of hospital stay was at least arithmetically shorter for those receiving parenteral nutrition (by four to six days). There was a reported “significant less” postoperative complication rate in the parenteral nutrition recipients in one of these trials,⁴⁰ but the specific numbers are unavailable. In the third trial³⁹ the use of parenteral nutrition was associated with an increase in radiologically confirmed anastomotic leaks. These data are too preliminary to conclude whether or not parenteral nutrition is beneficial when used in patients who have undergone colorectal surgery.

Three centres assessed the value of parenteral nutrition in patients undergoing surgery for various gastrointestinal malignancies^{41–43}; two found no effect whatsoever.^{41–42} The West German study⁴³ is, perhaps, the most often cited study supporting the use of parenteral nutrition. Muller *et al* found reductions in postoperative mortality (19% v 5%) and major morbidity (22% v 11%) associated with parenteral nutrition. Not mentioned in the paper, however, was a second treatment group, receiving a different parenteral formulation, which was dropped from the study before its completion (J Muller,

personal communication). Furthermore, the patients were stratified according to tumour site, and the differences were only present in those with gastric and oesophageal malignancies.⁴⁴ The major cause of mortality and morbidity in this second group was anastomotic leakage, which essentially disappeared in both groups when an anastomotic stapler was used (J Muller, personal communication).

Table 1 gives details of the patients with upper gastrointestinal malignancies participating in the remaining perioperative parenteral nutrition trials.^{45–51} Only the differences between the incidence of wound infections seen in the Cardiff study were significant.⁴⁵ In five of seven studies, however, the mortality was better in the recipients of parenteral

Table 1 Perioperative parenteral nutrition in upper gastrointestinal cancer surgery

Reference	Treatment	(n=)	Survival (%)	Complications (%)
45	Parenteral nutritional support 5–7/6–7	(38)	32 (84)	14* (40)
	Control	(36)	28 (78)	30* (83)**
46	Parenteral nutritional support 28/0	(12)	11 (91)	6* (50)
	Enteral 28/0	(12)	10 (83)	12* (100)
47	Parenteral nutritional support 6–8/6–7	(25)	24 (96)	1 (4)
	Enteral 6–8/6–7	(27)	23 (85)	4 (15)
48	Parenteral nutritional support 0/18	(18)	18 (100)	0 (0)
	Control	(16)	15 (94)	5 (31)
49	Parenteral nutritional support 5–7/6–7	(10)	10 (100)	0 (0)
	Control	(5)	5 (100)	1 (20)
50	Parenteral nutritional support 7–10/7–10	(10)	10 (100)	“More”
	Parenteral nutritional support 0/7–10	(10)	9 (90)	
	Control	(10)	9 (90)	
51	Parenteral nutritional support 14/0	(8)	8 (100)	3 (38)
	Control	(7)	7 (100)	4 (57)

The numerator of the fraction indicates days of preoperative nutritional support, the denominator days of postoperative support; *numbers of complications assumed one complication per patient; ** $p < 0.05$.

nutrition, and in five of six other reports a lower morbidity was also associated with the use of parenteral nutrition. Parenteral nutrition may, therefore, provide a small benefit, but the numbers of patients studied may have been inadequate to show this statistically (type I error).

To obtain some data concerning potential cost and benefit the reported morbidities and mortalities were weight averaged. The total postoperative complication rates were calculated to be 54% (control) and 22% (recipients of parenteral nutrition). In Cardiff and West Germany about 40% of the complications were minor and were reduced by about 75% using parenteral nutrition; the major complication rate was roughly halved. Using cost data derived by Twomey and Patching,⁵² the calculation outlined in Table 2 can be made. From a cost perspective, the overall result seems to make little difference. It could be argued that for an extra \$200 per patient, substantial pain and suffering is avoided (assuming the extra postoperative complications in some constitute more pain and suffering than preoperative parenteral nutrition in all).

Weight averaging the survival statistics indicates that the postoperative mortality may be reduced from 14 to 7%. This must be taken in the context of the underlying disease. The natural history of these operated malignancies is that just under 50% of the patients die in the first year, 50% in the next year, and most of the remainder in the next two to three years.^{53 54} Assuming that preoperative parenteral nutrition has no influence on this natural history, survival curves can be constructed (Table 3). As

Table 2 Cost effectiveness of providing parenteral nutrition in surgical patients with upper gastrointestinal cancer

Assumptions:

- 1 Ten days preoperative parenteral nutritional support to all patients
- 2 Provision of parenteral nutritional support will reduce complication rates
 - Minor complications: 20% without parenteral nutritional support, 5% with parenteral nutritional support
 - Major complications: 30% without parenteral nutritional support, 15% with parenteral nutritional support

3 Costs

- (i) One day hospital stay with total parenteral nutrition \$800
- (ii) Minor complication \$2000
- (iii) Major complication \$50 000

Costs of providing parenteral nutritional support to 100 patients:	
100 patients receiving 10 days each	\$800 000
Reduction of 15% in minor complications	-30 000
Reduction of 15% in major complications	-750 000
Net cost	\$20 000

Table 3 Difference in long term survival using preoperative parenteral nutrition in upper gastrointestinal malignancies (expressed as percentage)

Time period	Cumulative mortality*	
	Parenteral nutritional support used	Parenteral nutritional support not used
Perioperative	7.0	14.0
End of year 1	53.5	57.0
End of year 2	76.8	79.5
End of year 3	86.0	87.1
End of year 5	90.7	91.4

*Assumes all surgical survivors in both groups have following mortality: 1 year 50%; 1-2 years 25%; 2-3 years 10%; 3-5 years 5%; "cure" 10%.

only 10% of these patients are predicted to be cured, the 7% reduction in operative mortality only provides 0.7% of cured patients. For the average patient going to surgery provision of parenteral nutrition will give an additional two months of life (Table 4).

Trials of enteral feeding have also been conducted for perioperative patients. The liquid diets provided no particular advantage over routine bowel preparation.⁵⁵⁻⁵⁸ In fact, in one of these studies the recipients of the elemental diets had more complications and a longer hospital stay.⁵⁸ Two other trials evaluated the use of these residue free liquid diets as "medical colostomies" in patients undergoing anorectal surgery.^{59 60} Although there was a reduced analgesic requirement associated with the use of the liquid feeding,⁵⁹ the cost of the diet is greater than the cost of the one additional daily injection.

Several prospective randomised controlled trials of immediate postoperative small intestinal feedings

Table 4 Projected No of patient months of survival

Time period	Parenteral nutrition patients		Control patients	
	Deaths (%)	Patient months of life*	Deaths (%)	Patient months of life*
Postoperative (1 month)	7.00	0.035	14.00	0.070
1-12 months	46.50	3.023	43.00	2.795
13-24 months	23.25	4.185	21.50	3.870
25-36 months	9.30	2.790	8.60	2.580
37-60 months	4.65	2.232	4.30	2.064
"Cure"	9.30	16.740	8.60	15.480
Total	100.00	29.005	100.00	26.859

*Calculated by assuming average duration of life was a time halfway between beginning and end of time period; cured patients assumed to live average total of 15 years.

showed improvements in nitrogen balance.⁶¹⁻⁶³ Unfortunately, these studies, as well as a fourth,⁶⁴ failed to show a concomitant reduction in postoperative complications. Two of these trials found that the recipients of the tube feedings required five to six days less of intravenous fluids.^{62 64} The extra cost of placing the tube (about \$150) more than compensates for the small differences in the cost of a litre of each solution (\$21 for intravenous, \$15 for enteral). Three of these trials⁶¹⁻⁶³ considered the effect of these feedings on duration of hospital stay; while two found no difference, one⁶¹ reported a reduction of five days. Clearly, the savings to be gained by such a reduction in hospital stay would more than compensate for the expense incurred. It still remains to be confirmed, however, whether these feedings will reduce hospital stay.

In support of the notion that such feedings may be beneficial after trauma nocturnal nasogastric tube feedings of a liquid diet were shown to promote faster rehabilitation in "very thin" (two standard deviations below the mean) elderly women with hip fractures.⁶⁵ This effect was not seen in the better nourished patients.

Inflammatory bowel disease

Two trials of parenteral nutrition in inflammatory bowel disease (Crohn's disease or ulcerative colitis, or both) failed to show any clinical effect of this form of treatment.^{66 67} Both these studies were conducted on patients with active disease.

Two trials of enteral nutrition in Crohn's disease have been reported.^{68 69} In one, a crossover trial, there was no appreciable difference in clinical activity index when the patient was on a liquid nutritional supplement.⁶⁸ In the other a four week course of an elemental diet was as effective as corticosteroids in controlling acute bouts of Crohn's enteritis. The patients in the group given the elemental diet did not consume any food other than the elemental diet for two weeks; even including this saving the cost of the elemental diet would be 33% more than that of corticosteroids and food (Table 5).

None of these trials addresses the issue of patients who are long term nutritional cripples because of their inflammatory bowel disease.

Special amino acid preparations

Two special amino acid formulations have become available: essential amino acids (EAA) in renal failure; and branched chain amino acids (BCAA) in hepatic encephalopathy. (BCAA has also been advocated for physiologically stressed patients, but

Table 5 Cost comparison of corticosteroids and elemental diet in treating Crohn's disease

Item	Cost* (in US dollars)	
	Elemental diet	Corticosteroids
Corticosteroid		16
Food (two weeks)		140
Corticosteroid complication		750
Elemental diet	1215	
Total	1215	906

*Assumes: (i) Steroids given for 12 weeks in tapering doses 50 mg/day to 20 mg/day, then discontinued shortly thereafter; (ii) food costs \$10/day; (iii) probability of corticosteroid complication estimated (probably excessively) to be 10% for "minor" (cost=\$2000) and 1% for "major" (cost=\$50 000); (iv) elemental diet costs \$15/litre (1 litre on day 1, 2 litres on day 2, then 3 litres on days 3-30).

this indication will not be considered in the absence of prospective randomised controlled trials.) Two distinct issues are raised in the use of these preparations, questions which are often blurred by study designs. The first is whether the particular preparation is, in itself, effective (as a "medication") in treating these disease states; the second is whether the addition of a programme of nutritional support (including calories, vitamins, etc.) is more effective.

ESSENTIAL AMINO ACIDS

Four trials have assessed the value of EAA in acute renal failure⁷⁰⁻⁷³ (Table 6). In the largest study there was a considerable improvement in survival from the acute episode (75% v 44%), although only an

Table 6 Use of essential amino acids in acute renal failure

Reference	Treatment (n=)	Survival	
		Acute+ (%)	Discharge (%)
70	47% D+EAA (28)	21 (75)*	17 (61)
	50% D (25)	11 (44)	10 (40)
71	47% D+EAA (11)	6 (55)	4 (36)
	47% D (9)	5 (56)	4 (44)
72	36% D+EAA (7)	5 (71)	5 (71)
	36% D+ENAA (9)	3 (33)	3 (33)
73	37.5% D (7)	2 (29)	2 (29)
	41% D+EAA (3)	NS	0 (0)
	43% D+ENAA (2)	NS	0 (0)
	44% D (1)	NS	0 (0)

EAA=essential amino acids; ENAA=essential and non-essential amino acids; D=dextrose; NS=not stated. *Survived acute episode renal failure. *p<0.05.

Table 7 Use of Branched chain amino acids in hepatic encephalopathy

Mode of administration	Reference	Treatment	(n=)	Survival	Improved hepatic encephalopathy
Parenteral	74*	BCAA Standard amino acid formulations No treatment	(15)†	Not factor	Yes No No
	75	BCAA Parenteral nutritional support Dextrose (high concentration solution) + Neomycin	(30) (29)	25 (83%)‡ 13 (45%)	23 (77%)†† 13 (45%)
	76	BCAA Neomycin	(NS) (NS)	NS NS	33 hours†† 71 hours**
	77	BCAA Parenteral nutritional support BCAA Parenteral nutritional support + lactulose Lactulose	(8) (8) (15)	NS NS NS	8 (100%) 8 (100%) 12 (80%)
	78	BCAA Parenteral nutritional support Dextrose (high concentration solution) + lactulose	(17) (17)	14 (82%) 13 (76%)	12 (71%) 8 (47%)
	79	BCAA Parenteral nutritional support Dextrose (high concentration solution) /Lipid	(25) (25)	15 (60%) 20 (80%)	14 (56%) 12 (48%)
	80	BCAA Parenteral nutritional support Dextrose (high concentration solution)	(10) (10)	8 (80%) 9 (90%)	7 (70%) 6 (60%)
	81*	60 g Intact protein, 10 g BCAA 60 g Intact protein	(6)†	Not factor	0 (0%) 0 (0%)
	82*	40 g Intact protein, 30 g BCAA 40 g Intact protein 45 g BCAA 40 g Intact protein 80 g Intact protein	(NS) (NS) (NS) (NS)	Not factor Not factor	Better Better Baseline Worse
	83	20 g Intact protein, 30 g BCAA 50 g Intact protein	(4)†	NS	No difference
	84	30 g BCAA Placebo	(7)†	NS	3 (43%) 2 (28%)
	85	40 g Intact protein, Incremental addition of 20 g BCAA 40 g Intact protein, Incremental addition of 20 g Intact protein	(8)†	NS	No difference
Enteral					

Table 7 - *cont.*

Mode of administration	Reference	Treatment	(n=)	Survival	Improved hepatic encephalopathy
	86	20 g Intact protein. Incremental addition of 20 g BCAA	(14)	NS	13 (93%) ^{††}
		20 g Intact protein. Incremental protein of 20 g Intact protein	(12)	NS	5 (42%)

BCAA= Branched chain amino acids (Formulations may be pure branched chain amino acids or branched chain amino acid enriched).
NS=not stated.

*Patients with latent hepatic encephalopathy, measured by psychometric testing.

†Study design crossover rather than randomisation to one or other treatment arm.

‡p<0.01.

††p<0.05.

**Improvement in hepatic encephalopathy calculated as time for hepatic encephalopathy to resolve

arithmetically better hospital discharge survival rate (61% v 40%) in those receiving EAA.⁷⁰ This effect was especially noticeable in those patients who required dialysis. Surprisingly, in a similar protocol, evaluating only patients who required dialysis, these data could not be reproduced.⁷¹ A third small trial⁷² showed an arithmetic trend in the same direction as the first,⁷⁰ in the smallest of all the studies to be discussed in this paper (six patients divided into three treatment arms) there were no survivors.⁷³

These acute renal failure protocols are also difficult to interpret because of the treatment given to the control groups. In all four studies those not receiving amino acids were given high concentrations (usually even higher than those given to patients receiving amino acids) dextrose infusions. This osmotic load might be a problem in patients who are oliguric.

If EAA solutions really do save lives in acute renal failure they should be used, but at present, this has not been confirmed. We will need at least one more large study to attempt to settle the issue. Ideally it should include two groups receiving the essential amino acids (one with and one without large concentrations of dextrose to address the question of the addition of nutritional support), and a control group receiving truly standard care.

BRANCHED CHAIN AMINO ACIDS

A large number of prospective randomised controlled trials have addressed the issue of the use of BCAA in hepatic encephalopathy (Table 7).⁷⁴⁻⁸⁶ These studies usually used different BCAA preparations, some of which were BCAA only and others of which were enriched with BCAA.

The only trial to show a significant difference in survival was the multicentre American trial.⁷⁵ Two of the other studies in which survival data were

available found that arithmetical reductions in this variable were associated with the use of the BCAA solutions: interestingly, an earlier abstract (Hagenfeldt *et al.* Fourth symposium in intensive care in hepatology and gastroenterology, 1981)⁸⁷ of one of these studies,⁷⁹ reporting on a larger number of patients(!), found that the reduced rate of survival was significant.

The seven parenteral trials do share one thing in common: in all, those receiving BCAA had at least an arithmetical improvement in hepatic encephalopathy. The probability of all seven studies showing the same arithmetical trend, if there was no therapeutic benefit or detriment to the BCAA solution, would be the same as having a coin come up either heads or tails seven times in a row; this probability is 0.016. If we are again observing type II errors intravenous BCAA solutions may have some potential therapeutic value in treating hepatic encephalopathy. (Although one of the enteral trials also showed a beneficial effect of BCAA feedings on encephalopathy when a BCAA based elemental diet was fed instead of protein for several weeks, the data from the other trials do not clarify the reproducibility of this observation.)

These parenteral trials do suffer from the same drawbacks discussed above as those for EAA and acute renal failure. Are BCAA solutions in and of themselves therapeutic, and what (if anything) is to be gained by adding a programme of parenteral nutritional support? Was the administration of high concentration dextrose solutions to the control group detrimental? (The 55% mortality in the cooperative trial⁷⁵ may have been excessive.) Are BCAA solutions more effective than the standard antiencephalopathic lactulose therapies, or neomycin?

The daily costs of these three agents at my

Table 8 Cost comparisons for treating hepatic encephalopathy*

Treatment Regimen	Dollar costs	Days of hepatic encephalopathy
Neomycin×4 days, BCAA×2 days to non-responder	56.40	3.45
Lactulose×4 days, BCAA×2 days to non-responder	70.40	3.45
BCAA×2 days, neomycin×4 days to non-responder	126.0	2.25

*Assumes: (i) efficacy and length of treatment of neomycin, rifamycin, lactulose, and branched chain amino acid solution as stated in text (optimistic estimate); (ii) no impact of hepatic encephalopathy treatment on mortality or duration of hospital stay; (iii) cost of neomycin, lactulose and branched chain amino acid solution as stated in text.

hospital are: neomycin (4 g) \$1.00; lactulose (200 g) (a large dose), \$5.10; intravenous BCAA solution (amino acid solution alone) (40 g), \$62.50. If these are equally effective it is obviously costly to use the BCAA solution. Table 8 makes a cost comparison, assuming that the BCAA solution is more effective (75%) than either lactulose or neomycin (60%), and, furthermore, that it only need be administered for two days instead of four. Even under these optimistic conditions, it is still more expensive to begin treatment with BCAA solutions. As is seen, the extra price may result in a shorter duration of encephalopathy. (These patients usually have complicated liver disease and other problems, and there is no reason to assume that the earlier resolution of encephalopathy will translate into a shorter hospital stay.)

Other prospective randomised controlled trials

Six studies have considered the use of parenteral nutrition in low birth weight infants;⁸⁷⁻⁹² in only one of these was there overt concomitant illness – respiratory failure.⁸⁷ Parenteral nutrition did not affect survival in any of the trials. Although there were fewer days with apnoea in a group of infants who received parenteral nutrition compared with those of the control infants,⁸⁸ in another trial the babies receiving parenteral nutrition had an overall increase in various complications.⁸⁹ As parenteral nutrition may be associated with more rapid weight gain could the use of it at least be associated with a shorter hospital stay, as weight is the discharge criterion in these children? In fact, faster weight gain was seen in four of the five reports for which this variable was measured (faster⁸⁸⁻⁹¹; no

difference⁹²). In spite of this there was no difference in overall duration of hospital stay in the three trials for which this information was available.⁸⁹⁻⁹¹

Three trials have assessed the use of parenteral amino acids in alcoholic hepatitis (with or without an energy source).⁹³⁻⁹⁵ Although the differences in survival in one (100% v 78%⁹³) were reported as significant, in fact, this is not the case when the calculation is corrected for the small numbers of patients ($p=0.13$). Two of the trials^{93 94} found a faster fall in the serum bilirubin concentration in association with the use of the amino acids, but it was not shown that this biochemical phenomenon correlated with any important clinical event.⁹⁴

Small trials of parenteral nutrition in burn patients⁹⁶ and those with acute pancreatitis⁹⁷ have been conducted. No differences between outcome were noted. Elemental diets were evaluated as treatment for asthma;⁹⁸ although favourable results were reported, based on a numerical improvement in a symptom score, the authors happened to have picked the only such symptom score in which the differences were significant.

Finally, one trial was conducted in patients with head injuries.⁹⁹ They were randomised to receive parenteral or enteral nutrition (via nasogastric tube feedings). A difference between survivals was observed, favouring the recipients of parenteral nutrition. From the study design, however, it was impossible to say whether parenteral nutrition was good or enteral nutrition bad. Based on the historical experience from the same institution,¹⁰⁰ it could be calculated that the enteral feeding was more likely to have produced an adverse effect than was parenteral feeding to have produced a beneficial one.¹⁰²

Inadequate bowel syndrome

There are patients in whom the capacity to maintain their nutritional state is permanently lost. Although the term "short bowel syndrome" is often applied, the intestine is sometimes anatomically present (albeit non-functional), and the term "inadequate bowel syndrome" seems to be more appropriate. Patients so diagnosed will, by definition, die of starvation unless programmes of nutritional support are given. It would be unethical to conduct prospective randomised controlled trials to prove that life is prolonged. It is assumed that the parenteral nutrition is effective, and the cost of these programmes therefore becomes a societal issue.

Some patients do not have permanent inadequate bowel, but they can be predicted to have (or have already shown) protracted problems. A special example of this is growth retardation in adolescents

with various gastrointestinal disorders. Again, the problems inherent in growth retardation are well defined, and nutritional support during these growth years is known to reverse the problem.

This does lead to the more general issue of deciding how long is too long to go without adequate nutrition. It is clear from our clinical experience that any well nourished subject can tolerate several days of nutritional deprivation. What we don't know is how long this can go on before the problems presented by the malnutrition detrimentally affect those of the underlying disease. The failure of most of the prospective randomised controlled trials to show an effect suggests that in many of these patients the impact of the associated malnutrition is small. To make rational decisions about these expensive nutritional treatment regimens we need to know how long is too long to go without nutritional supplementation.

Conclusions

The above analysis was of prospective randomised controlled trials. The studies, however, were grouped in an attempt to find possible areas of benefit. This is, in effect, a retrospective review of the prospectively collected data. The analogy to the coin flip should be modified; a more appropriate consideration would be that I have reviewed a sequence of coin flips, found parts of that sequence where the coin flips seemed to have defied statistical probability, and then asked if the coin was somehow loaded. In fact it may or may not have been. Retrospective reviews must be confirmed by prospective trials.

It is obvious that nutritional support supports nutrition. It is also clear that most of the attempts to prove that this support can be translated into beneficial clinical outcome have not been successful. This should not be interpreted as meaning that no benefit exists. Many of the trials studied small numbers of patients; less than significant differences might have been missed. On the other hand, it must be apparent that nutritional support will not provide huge benefits. We must approach nutritional support with the same clinical scepticism and objectivity that we approach other proposed treatment regimens. Certainly, if nutritional support had come on the market as a drug, the Food and Drug Administration in the United States would never have accepted it. Data from large prospective randomised controlled trials proving or disproving the various proposed applications of nutrition support are needed; its cost effectiveness must then be established where clinical efficacy is shown.

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