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Nutrition Society Symposium on ‘End points in clinical nutrition trials’ Death, morbidity and economics are the only end points for trials

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In order to determine whether surrogate markers predict clinical outcome, randomized controlled trials (RCT) of nutrition support v. no nutrition support that have reported at least one clinical outcome (mortality, infections, total complications, or duration of hospitalization) and at least one nutritional outcome (energy or protein intake, weight gain, N balance, albumin, prealbumin, transferrin, three anthropometric measures, skin testing, lymphocyte count) were assessed for concordance. If changes in nutritional markers predict clinical outcome, changes in both outcomes should go in the same direction. Concordance is defined as both outcomes changing in the same direction or both outcomes showing no difference. Discordance is defined as one outcome changing and the other not (partial) or both outcomes changing in opposite directions (complete). Ninety-nine RCT were identified, of which most were underpowered to see statistically significant changes, especially in clinical outcomes. Thus, the results were analysed only in relation to the direction of the respective changes in outcomes. Forty-eight comparisons (4×12) were made. The rates of concordance were $\leq 50\%$ in forty-one of forty-eight comparisons; the rate was never $>75\%$. A complete discordance rate of $\geq 25\%$ was present in forty-three ($\geq 50\%$ in thirteen) of the forty-eight comparisons. The discordance was usually a result of the nutritional outcome being better than the clinical outcome. Changes in nutritional markers do not predict clinical outcomes. Before adopting any surrogate marker as an end point for a clinical trial, it has to be known that improving it will result in patient benefit.

Nutrition support: Outcomes: Surrogate outcomes: Intermediate outcomes: End points

‘In order for a difference to be a difference, it must make a difference.’

Approximately 70 years ago Studley (1936) noted that patients who had lost $\geq 20\%$ of their body weight before surgery for peptic ulcer disease had a higher mortality than patients with the same condition but more modest weight losses. Subsequent observational studies have confirmed this association between malnutrition and an adverse clinical outcome in patients with other diseases (Buzby *et al.* 1980; Reinhardt *et al.* 1980; Baker *et al.* 1982). It is also known that even if healthy individuals are deprived of adequate nutrients for a long enough period of time adverse clinical events resulting from starvation will

develop (Keys, 1962). For both these reasons it has seemed reasonable to provide nutrition support to patients who are (or are at risk of becoming) malnourished.

The first form of such artificial nutrition support (parenteral) became available in the 1960s (Rhoads *et al.* 1981). These intravenous, and subsequent enteral, formulations were marketed as ‘foods’; as such, ‘efficacy’ was established by showing that nutritional status was maintained (Dudrick *et al.* 1968). However, it must be appreciated that while such maintenance may be appropriate in healthy growing organisms with very limited nutritional reserves (e.g. otherwise healthy newborn animals or infants), the intent of nutrition support is to improve the clinical outcome of a wide variety of diseases

Abbreviations: RCT, randomized controlled trials.

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(Dudrick & Ruberg, 1971). From this perspective, variables of nutritional maintenance (e.g. body weight or N balance) become intermediate or surrogate end points.

It is a well-established principle of evidence-based medicine that it cannot simply be assumed that improving intermediate end points translates into clinical improvement (reduction in mortality or morbidity). For example, patients with chronic rheumatoid arthritis frequently have anaemia; however, there is no reason to believe that simply increasing the Hb concentration will have any impact on the ravages of the joint disease. Before improvements in surrogate outcomes can be accepted as predictors of clinical benefits, it must at least be demonstrated (in randomized controlled trials (RCT) comparing intervention with no intervention) that altering those intermediate outcomes is associated with a similar alteration in the clinical outcomes.

Such supportive evidence does exist for some intermediate outcomes. For example, a mathematical analysis comparing surrogate and clinical outcomes in randomized treatment trials of patients with AIDS has demonstrated that, at least over the long-term, titres of human HIV RNA are a reliable surrogate marker for survival (HIV Surrogate Marker Collaborative Group, 2000). It is the intention of the present paper to compare the clinical and nutritional outcomes in RCT that have compared nutrition support with no nutrition support and have provided data that can be evaluated.

Concordance and discordance

As noted, a necessary condition for accepting the ability of a surrogate marker to predict a clinical outcome is the presence of a parallel or concordant effect. In other words, a study that shows an improvement or adverse effect in the surrogate marker also has to show the same effect in the clinical outcome, and a study that fails to show a difference in one outcome will also fail to show a difference in the other. 'Discordance' will be defined as a situation when the two outcomes do not agree. These concepts are illustrated in Table 1. If discordance exists, the ability of the nutritional outcome to predict the clinical outcome cannot be relied on.

A systematic review of the nutrition literature has been undertaken to identify RCT that have compared parenteral nutrition, intravenous protein-sparing therapy (the intravenous delivery of amino acids with relatively low amounts of non-nitrogenous energy) or enteral nutrition with no

nutritional intervention (true control) and have reported at least one clinical and one nutritional outcome; the methodology of the literature search has been previously described (Koretz *et al.* 2001). The clinical outcomes of interest were mortality, infectious complications, total (including infectious and non-infectious) complications and duration of hospitalization. (Although cost issues would also be of interest, very little such information was available from the RCT.) The nutritional outcomes that were sought included intake of energy or protein, change in body weight, N balance, serum albumin, anthropometrics (triceps skinfold thickness, mid-arm circumference and mid-arm muscle circumference), other visceral proteins (transferrin, prealbumin), skin tests and total lymphocyte counts. A total of twenty-one RCT of enteral nutrition, fifty-nine RCT of parenteral nutrition and nineteen RCT of protein-sparing therapy were identified; they are listed in the Appendix.

All the RCT that have reported a particular clinical outcome and a particular nutritional outcome were entered in a table constructed like the example shown in Table 1. Since there were four clinical outcomes and twelve nutritional outcomes, forty-eight such tables were created. However, many of the individual trials contained relatively few subjects; when only statistically significant differences were considered, the RCT tended to cluster in the middle cell of Table 1 (concordance). For a few of the nutritional outcomes (e.g. body weight or N balance), significant differences were commonly found in all the trials, irrespective of size, so that the RCT tended to cluster in the upper middle cell of Table 1 (partial discordance–nutritional outcome better than clinical outcome). The former situation created an appearance of concordance and the latter one of discordance when the real issue may have been the size of the study. Since statistically significant differences (particularly in underpowered trials) would be an unreasonable expectation, the primary analysis was performed considering only arithmetic differences. (In this way, when N balance was significantly improved, even an arithmetically-better clinical outcome would result in the RCT being judged as concordant.) The results of these primary analyses will be discussed.

It was decided *a priori* that when a trial included more than one treated group all the results would be pooled and compared with the control group (to avoid an over-representation of such studies in the analysis). The only exception to this rule was to be reports in which one group received enteral nutrition and another group received

Table 1. Nutritional v. clinical outcomes in randomized control trials

		Clinical outcome		
		Better than control	No different than control	Worse than control
Nutritional outcome	Better than control	C	PD–N better	CD–N better
	No different than control	PD–C better	C	PD–N better
	Worse than control	CD–C better	PD–C better	C

C, concordance; PD, partial discordance; CD, complete discordance; N better, nutritional outcome better than clinical outcome; C better, clinical outcome better than nutritional outcome.

parenteral nutrition; there was only one such report (Fletcher & Little, 1986). Some papers failed to provide numerical data and only noted that there was 'no difference' between the two groups; in such cases it was assumed that there were no arithmetic differences.

If reliance is going to be placed on these surrogate markers to predict the clinical outcome, the presence of very high concordances must be demanded (as this situation is analogous to the predictive value of a test). Simple mathematics indicates that if there is no relationship at all between clinical and nutritional outcomes 33% of the RCT should appear to be concordant (since three of the nine cells are concordant).

Are nutritional and clinical outcomes concordant?

Not every RCT reported each of the four clinical and twelve nutritional outcomes. The number of trials that reported each one is listed in Table 2, along with the percentage that showed statistically significant or at least arithmetical differences favouring the treated group. As can be appreciated, the nutritional outcomes were improved (at least arithmetically) in 57–100% of the trials, whereas the clinical ones were improved in 32–55%. This observation alone indicates that there will be some discordance.

The actual rates of concordance and discordance (partial and complete) are summarized in Table 3. The absence of a rate in a particular column indicates that none of the RCT provided data for such a combination. The rates of

concordance were rarely found to be >50%, and never >75%. (The two highest rates (67%, 75%) were observed in situations in which only three and four RCT were available.) The rates of discordance were almost always a result of the nutritional outcome being better than the clinical outcome. It is perhaps even more disconcerting that the rates of complete discordance (the nutritional effect and the clinical effect going in opposite directions) were often almost as high (and occasionally higher) as the rates of concordance.

Why is there so much discordance?

Probably the major reason why surrogate outcomes are used is the belief that the outcome is pathophysiologically important in the disease. It is reasonable to view the titre of HIV RNA in this way; individuals with larger numbers of viral particles in the circulation will be more likely to have more lymphocytes subsequently infected. While it is known that malnourished patients have poorer outcomes than well-nourished patients with the same underlying disease, such an association does not establish causation. It may be that the malnutrition independently contributes morbidity; it may also be that the malnutrition is a reflection of worse disease. In the latter scenario malnutrition is simply a messenger telling the observer that a bad situation is present; shooting the messenger will not alter the content of the message. Given the discordance in the nutritional and clinical outcomes, it would seem more reasonable to believe this latter scenario, i.e. that the association is not causative.

This hypothesis has been tested in another arena. It is known that patients with hypoalbuminaemia have poorer clinical outcomes (Koretz, 1995). If albumin was itself responsible, improving the albumin level should result in better clinical outcomes. Curiously, the only debate in the literature is whether or not albumin infusions are harmful (Cochrane Injuries Group Albumin Reviewers, 1998; Wilkes & Navickis, 2001).

Conclusions

Nutrition support may be useful in maintaining nutritional status. However, this action does not necessarily translate into meaningful clinical gain. Since this therapy is used as an adjunct for sick patients, it is the clinical gain that is the aim. In order to assess the ability of enteral or parenteral nutrition to alter the clinical course of any underlying disease process in a favourable way, it must be shown that its use will improve mortality or morbidity (and does so at a cost that is affordable in a resource-constrained environment).

There are hard data that demonstrate that such improvements cannot be assured simply because various surrogate nutritional outcomes are altered. Given this experience, it is necessary to be sceptical about the utility of other surrogate outcomes; before any surrogate marker is adopted as a desirable end point of a clinical trial, it must be known that changing it will provide a clinical benefit to the patient.

Table 2. Impact of nutrition support on clinical and nutritional outcomes

Outcome	No. of studies	Improved by nutrition support			
		Statistically significant		At least arithmetic	
		<i>n</i>	% total	<i>n</i>	% total
Nutritional					
Energy intake	34	29	85	30	88
Protein intake	19	17	89	18	95
Weight gain	61	33	54	51	84
N balance	43	39	91	43	100
Albumin	62	7	11	35	57
TSF thickness	32	8	25	20	63
MAC	16	3	19	11	69
MAMC	22	5	23	17	77
Transferrin	28	11	39	21	75
Prealbumin	23	8	35	21	91
Skin tests	12	2	17	8	67
TLC	9	0		6	67
Clinical					
Mortality	87	1	1	36	41
Infections	62	2	3	20	32
Total comp	59	4	7	24	41
Dur'n hosp	38	1	3	21	55

TSF, triceps skinfold; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; TLC, total lymphocyte count; comp, complications; dur'n hosp, duration of hospitalization.

Table 3. Rates of concordance and discordance between various clinical and nutritional outcomes

Table of Rates of Concordance and Discordance between Clinical and Nutritional Outcomes						
Outcome	No. of trials	Concordance	Partial discordance		Complete discordance	
			Nutrition better*	Clinical better†	Nutrition better*	Clinical better†
Energy intake						
Mortality	31	42	29		29	
Infections	22	32	23		45	
Total comp	20	30	20		50	
Dur'n hosp	18	44	17		39	
Protein intake						
Mortality	18	22	33		39	6
Infections	13	23	23			54
Total comp	9	11	33		56	
Dur'n hosp	8	50	25		25	
Weight gain						
Mortality	56	40	23	2	29	5
Infections	36	31	8		56	6
Total comp	34	41	12	3	38	6
Dur'n hosp	14	50	7	14	21	7
N balance						
Mortality	36	36	42		22	
Infections	30	43	17		40	
Total comp	31	48	16		35	
Dur'n hosp	25	56	8		36	
Albumin						
Mortality	56	29	18	20	25	9
Infections	37	38	16	8	32	5
Total comp	35	43	11	9	29	9
Dur'n hosp	24	50	8	4	21	17
TSF thickness						
Mortality	30	27	10	20	33	10
Infections	24	13	25	4	42	17
Total comp	18	22	17	6	28	28
Dur'n hosp	8	63		13	13	13
MAC						
Mortality	16	50	17	13	13	7
Infections	12	33	17	8	25	17
Total comp	12	42	17	17	8	17
Dur'n hosp	4	50			25	25
MAMC						
Mortality	21	24	19	5	48	5
Infections	19	11	11	16	63	
Total comp	10	30	10	10	50	
Dur'n hosp	5	40	20		40	
Transferrin						
Mortality	26	35	19	19	23	4
Infections	17	41	12		41	6
Total comp	17	29	6	24	35	6
Dur'n hosp	12	25	8		42	25
Prealbumin						
Mortality	18	33	39	6	22	
Infections	16	38	6		56	
Total comp	15	60	13		27	
Dur'n hosp	9	44			56	
Skin tests						
Mortality	12	42	17	17	25	
Infections	8	25	38	13	25	
Total comp	5	60	20	20		
Dur'n hosp	5	40	20	20	20	
TLC						
Mortality	6	33	17	33	17	
Infections	3	67			33	
Total comp	7	57	14		29	
Dur'n hosp	4	75				25

Comp, complications; dur'n hosp, duration of hospitalization; TSF, triceps skinfold; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; TLC, total lymphocyte count.

*The effect of the therapy was more beneficial on the nutritional outcome than on the clinical outcome, e.g. if the clinical outcome was 'no different', the nutritional one was 'better' or the nutritional outcome was 'no difference' while the clinical outcome was worse.

†The effect of the therapy was more beneficial on the clinical outcome than on the nutritional outcome, e.g. if the nutritional outcome was 'no different', the clinical one was 'better' or the clinical outcome was 'no difference' while the nutritional outcome was worse.

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Appendix

Randomized trials that have reported both clinical and nutritional outcomes

Enteral nutrition:

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Parenteral nutrition:

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