Efficacy of Nutritional Support: Evidence-Based Nutrition and Cost-Effectiveness

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Introduction

The treatment of diseases encompasses a nutritional approach from ancient times, however it was only 200 years ago that the fundamentals of biochemistry, physiology and organic chemistry were firmly solidified as science. New expanding scientific concepts allowed the general knowledge that macro- and micronutrients play an important role in the proper and healthy development of the body. The deleterious consequences of different states of total or partial starvation, associated or not with trauma, infections or stress in any other form were well recognized.

Nutrition acquired the reputation of a sound biomedical science with a major impact on public health care.

However, with the advent of modern technology and new-generation drugs applied to surgical and medical practices, interest in hospital clinical nutrition decreased.

After the impressive experimental results obtained with total parenteral nutrition (TPN), it was discovered that nutritional therapy (NT) was a lifesaving procedure [1]. In this scenario, the use of parenteral and enteral nutritional therapy in the clinical setting was stimulated and prompted in unprecedented numbers.

The 1970s were devoted to understand the methods and complications of NT. Many reports praised the advantages of NT compared to historic control series or noncontrolled studies. NT was associated with better outcome in
terms of morbidity and mortality in patients suffering from low protein-calorie intake and hypermetabolic status.

Within the following decade, randomized, controlled clinical trials were not able to show the same enthusiastic results previously observed. Biochemical and immunological parameters could react positively with NT, but clinical outcome results changed moderately. Apparently, morbidity and mortality could be the final result of the whole clinical condition and care of the patient. It became clear that nutritional intervention was an adjuvant part of total patient care.

In the last 10 years, carefully designed clinical trials and meta-analyses comprising thousands of cases were successful in showing that nutritional intervention was able to reduce the average length of hospital stay (ALOS), the number of days in the intensive care unit (ICU) and on artificial respiration in critical care patients.

Concurrently, in the last 20 years the cost of medical care has been increasing worldwide and efforts are aimed at reducing the health bill. There are never enough resources to provide all of the health services known to be beneficial and choices have to be made. The cost of providing NT can be significant. Economic analyses can be used to compare the actual contribution of NT with the resources required to produce it.

The purpose of this chapter is to analyze concisely the efficacy and cost benefit of NT based on scientifically published evidence.

**Why Nourish?**

Roughly it could be said that NT is indicated for those patients who should receive a determined daily amount of macro- and micronutrients, but have difficulties in partially or totally achieving these requirements.

Malnutrition can be understood as a consequence of a metabolic imbalance caused by disease with a normal or higher protein-calorie demand, with an inadequate offer of nutrients and a potential alteration in body composition and organ functions.

Malnutrition has never been shown to improve the outcome of any disease. On the contrary, it is associated with a decrease in immune functions, increases the susceptibility to infections, and delays wound healing among other well-known functional disabilities.

The consequence of the failure to fulfill the calorie, protein, vitamin, mineral and oligo-element requirements of patients is progressive malnutrition.

Hospital malnutrition, namely the malnourished state of hospitalized patients, is highly and universally present [2]. The prevalence of hospital malnutrition is estimated to range from 15 to 70% and is addressed by more than 150 studies worldwide. Most published reports are derived from data collected by screening patient charts for the presence of nutritional risk
factors associated with morbidity. Usually risk factors pertain to medical and diet history, anthropometric measures (height, weight and recent weight loss) and selected laboratory values (serum albumin, hemoglobin, hematocrit, total lymphocyte counts). The available studies were performed in urban public teaching hospitals, and also in small town communities, private and pediatric hospitals. In the United States, hospital malnutrition was found to be prevalent in 30–50% of government-supported hospitals and also in other community institutions. Of the patients admitted to hospitals for gastrointestinal surgery, 3–12% were severely malnourished according to a meta-analysis of 18 controlled trials [3]. In Italy, it was observed that after prolonged hospitalization, the state of malnutrition worsened, and well-nourished patients had a decline in nutritional status [4].

This issue was analyzed in a specifically designed prospective multicentric study carried out in Brazil. In the multicentric Ibranutri cross-sectional study, performed by the Brazilian Society of Parenteral and Enteral Nutrition, each of 4,000 patients was evaluated for malnutrition using a subjective global assessment technique. It was found that 48.1% of patients in 25 hospitals of the Brazilian public health care system were malnourished, and in 12.6% this was severe [5]. Malnutrition was significantly related to the geographic origin of the patient (north/northeastern part of the country), age (>60 years old), and the presence of cancer and/or infection. The length of hospital stay at the time of nutritional assessment was a significant risk factor for malnutrition. 30.1% of the patients evaluated 2 days after admission had malnutrition and this climbed to 60.1% after 15 days in hospital. Clinical care patients were more severely malnourished than surgical patients (61 versus 39%, $p < 0.01$). The patients received nothing per mouth for 4 days on average. In a subgroup analysis of patients with digestive tract surgery, malnutrition was even worse [6]. In Latin America, the Federation of Latin America Societies for Parenteral and Enteral Nutrition conducted a survey of hospital malnutrition encompassing 12 countries and 9,233 adult patients from the public health system [7]. It has shown 50.2% of the patients were malnourished and in 12.6% severe malnutrition was found.

There are risk factors that may contribute to hospital malnutrition. The previous socioeconomic status of the patient may be responsible for the primary malnutrition. This condition may be aggravated by the disease per se, particularly those associated with hypercatabolism and wasting. Elderly and very young patients, chronic diseases, psychological reaction may also contribute to anorexia, organic malfunction and malnutrition. And last but not the least, there is a lack of awareness shown by the health care team of the patient’s nutritional status and intake. This was observed in the Ibranutri Study that less than 25% of the patients had some knowledge of nutritional status, but paradoxically 75% had easy access to a body weight scale [5].
In the US, the Nutritional Care Management Institute evaluated hospital malnutrition in 20 national hospitals encompassing 2,485 patients. It was found that 94.4% of the American patients had risk factors for malnutrition and they accounted for 95.5% of the total patient days. Those patients without risk factors stayed in the hospital around 10.5 days whereas those with 7 or more risk factors stayed an average of 18 days (Table 1) [8].

These results indicate that hospital screening programs for nutritional risk should be mandatory. The Brazilian Minister of Health, sensitized by the alarming information from the Ibranutri Study, passed a recommendation that nutritional screening and assessment should be routinely incorporated into the hospital care of all patients [9, 10].

### Consequences of Hospital Malnutrition

Malnutrition negatively affects the organic maintenance and body repair systems by impairing the ability of the immune system, the efficacy of enzymatic systems, and wound healing and inflammatory responses. It may also be associated with loss of muscle strength, increased incidence of bone

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**Table 1. Benefits of nutritional intervention for patients at risk**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis procedure</th>
<th>Hospital days saved</th>
<th>Decrease in ALOS,%</th>
<th>Annual saving per patient, USD¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deitel [37]</td>
<td>Intestinal fistula</td>
<td>7</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Collins et al. [38]</td>
<td>Colorectal surgery</td>
<td>8</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Askenazi [39]</td>
<td>Radical cystectomy</td>
<td>7</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Bastow et al. [40]</td>
<td>薄性髋関節骨折</td>
<td>7</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very thin patients</td>
<td>7</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Weinsier [41]</td>
<td>Burns</td>
<td>7</td>
<td>24</td>
<td>6,400</td>
</tr>
<tr>
<td>Smith et al. [42]</td>
<td>Intractable diarrhoea</td>
<td>26</td>
<td>37</td>
<td>14,750</td>
</tr>
<tr>
<td>Szeluga et al. [43]</td>
<td>Bone marrow transplant</td>
<td>3</td>
<td>8</td>
<td>1,436</td>
</tr>
<tr>
<td>Moore and Jones [44]</td>
<td>Major abdominal trauma</td>
<td>3</td>
<td>11</td>
<td>3,356</td>
</tr>
</tbody>
</table>

¹USD values reported are those for the years the study took place.
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fractures and pressure sores. The overall consequence is increased morbidity, mortality, length of hospital stay and consequently in hospital costs.

A cohort study was performed by the Ibranutri Study in all of Brazil, in order to correlate the patient’s nutritional status with the incidence of complications, mortality, and length of hospitalization. It comprised 709 patients assessed 72 hrs after admission into the hospital. The incidence of malnutrition was 34.2% at admission and the incidence of complications in the malnourished group was 27.0% versus 16.8% found in the nourished group (relative risk (RR) 1.60, confidence interval (CI) = 1.20–2.14). Infectious complications were significantly greater in malnourished patients (19.4 versus 10.1%; RR = 1.93, p < 0.01). The mortality rate was 7.3%; however, the death rate in malnourished patients was 12.4% versus 4.7% in the nourished group (RR = 2.63, p < 0.01; Fig. 1). The ALOS was 16.7 (24.5) in the malnourished patients versus 10.1 (11.7) in the nourished patients (Fig. 2). In this study a logistic regression model for the outcome variables, complications and mortality, has shown that malnutrition was an independent risk factor for the occurrence of both events [11]. It was also shown that malnutrition directly influenced the public health system costs.

The incidence of major infectious and noninfectious complications increased two- to sixfold in malnourished patients. The mortality rate could be two- to fourfold higher [12]. The treatment of malnutrition-related complications and the longer ALOS engender higher hospital costs.

Fig. 1. The Ibranutri Study: morbidity and mortality. From Correia and Waitzberg [6].
Fig. 2. The Ibranutri Study: malnutrition × length of stay. From Correia et al. [11].
The costs of malnutrition may be expressed directly (hospital charges) and indirectly (morbidity, ALOS, and mortality). Many available studies infer higher hospital charges due to longer ALOS, but the actual cost was prospectively measured by two North American studies. The charges for malnourished patients were calculated as being 75% higher than the cost of the average patient in a 300-bed small-town hospital (32% of hospital malnutrition). It was found that malnutrition cost the hospital an additional 19.4% [13, 14]. Malnutrition was responsible for 37.6% of the total cost of caring for patients in a 600-bed urban teaching hospital (56% malnourished patients of 100 consecutive admissions). The charges for malnourished patients were 117% higher than for the average patient [14, 15].

Although few hospitals track the severity of illness or nutritional risk, it becomes clear that the economic consequences of malnutrition are an important penalty to pay. Therefore in order to provide NT as soon as possible, it is important to recognize patients who are malnourished or at risk of developing malnutrition on admission or during diagnosis.

**Does Nutritional Therapy Make a Difference?**

Many advantages of NT have been described, such as an improvement in serial biomarkers, body composition and functional parameters. However, in order to prove that NT makes a positive difference, benefits and not only theoretical advantages are required. Prospective, randomized, controlled clinical trials (PRCTs) are the gold standard approach to demonstrate the benefits of treatment. However, PRCTs need large numbers of patients, are very difficult, time-consuming, costly to perform and may suffer from differences in study populations, nutritional formulas, dose used, and outcomes measured.

The clinical trial’s heterogeneity may compromise the meta-analysis used to summarize the results of NT, in addition to the difficulty of the investigators performing the meta-analysis to understand the basic issues, and defects in abstracting. In spite of these difficulties NT PRCT and meta-analysis studies are accepted as efficient forms to demonstrate clinical efficacy.

There are some special situations, where the beneficial role of NT is not disputed, since the natural history of these diseases is poor intestinal absorption and starvation. One example of intestinal failure or insufficiency is short bowel syndrome. Another example of an irrefutable indication for NT is malnutrition, due to an inability to eat caused by obstruction of the upper digestive tract. It is also well established that home NT is cheaper and safer than hospital NT [16].

However, in special situations the role of NT in clinical improvement becomes controversial.
The impact of preoperative TPN on major postoperative morbidity has been the object of many PRCTs. One of the best-designed studies available is the Veterans Administration Cooperative Study [17] that included 395 patients and could not show an overall benefit from TPN. After a careful analysis the VA study revealed a net benefit for TPN in severely malnourished patients [17].

In a comprehensive review of nutritional support in clinical practice sponsored by the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition, and the American Society for Clinical Nutrition, it was concluded that TPN provided preoperatively to malnourished patients was effective in reducing complications, whereas when TPN was provided routinely postoperatively, complications were increased by a similar amount [18]. Recently a meta-analysis found that there were 27 randomized trials in surgical patients that compared the use of TPN to standard care (usual oral diet plus intravenous dextrose). When the results of these trials were aggregated, there was no effect on mortality (risk ratio \(= 0.97\), 95% CI 0.76–1.24). There were fewer major complications in patients who received TPN, although there was a significant heterogeneity in the overall estimate (risk ratio \(= 0.81\), 95% CI 0.65–1.01). Studies that initiated TPN preoperatively demonstrated a trend to a reduction in complication rates but no difference in death rate, when compared with studies that initiated TPN postoperatively [19].

These data show that clinical trials and meta-analyses investigating the potential benefits of perioperative TPN for reducing the risk of surgery in malnourished patients have yielded controversial results.

Recently in Italy, it was shown that 10 days of preoperative TPN that is continued postoperatively was able to reduce the complication rate by approximately one third and to prevent mortality in severely malnourished patients with gastrointestinal cancer [20].

In a PRCT, preoperative EN compared to control (without EN) was associated with less wound infection (10.5 \(versus\) 37.2%) and shorter postoperative hospital stay (10 (2.8) \(versus\) 13 (3.4) days) [21]. For another population, namely critically ill patients, a meta-analysis has shown that TPN has no benefit and that it may increase complications and possibly mortality, except for severely malnourished patients, in whom complications are reduced but mortality is not [22]. A meta-analysis combining data from 8 PRCTs that compared the nutritional efficacy of early (within 72 h) EN and TPN in trauma and major postoperative patients determined that EN resulted in a twofold decrease in septic complications [23].

The issue of postoperative NT was recently addressed by an Italian study [24]. The authors found that for malnourished patients with gastrointestinal cancer, EN significantly reduced the complication rate and duration of postoperative hospital stay, when compared with parenteral nutrition, although parenteral nutrition is better tolerated than EN [24].
In inflammatory bowel disease, a meta-analysis pooled the results of 9 PRCTs to compare EN with steroids and 7 comparing elemental with nonelemental diets [25]. Steroids were found to be better than EN in inducing remission in active Crohn’s disease, however the overall remission rate after EN was about 60% higher than reported responses for placebos (20–30%), showing some primary therapeutic effect of EN in inflammatory bowel disease [26].

The primary impact of NT was also found to be suggestive in liver failure. A meta-analysis on 5 PRCTs administering parenteral branched chain amino acid solutions as part of the treatment of patients with acute hepatic encephalopathy determined a significant reversal of hepatic coma [27].

The more complex a clinical status became, the higher the number of metabolic variables involved. This is the case for critically ill patients subjected to infection and multiple organ failure. In this clinical setting, the use of enteral feedings enriched with immune-enhancing ingredients, known as immunonutrition, has been studied for the last two decades. Two meta-analyses tried to understand the immunonutrition role. The first meta-analysis with data from 11 PRCTs of patients with critical illness and cancer verified a decrease in the risk of major infectious complications and in the duration of hospital stay. Noteworthy was the absence of a difference in mortality, but a trend toward an increased risk of death ($p > 0.05$) in the immunonutrition group [28]. The second meta-analysis included 12 PRCTs with only critically ill patients. The results found confirmed the significant reduction in infection rate, ventilator days and length of hospital stay, but did not find a difference in mortality in the immunonutrition group, when compared to control standard enteral diets [29]. Recently, a nonblinded PRCT of critically ill patients with sepsis found a significant reduction in mortality (19.1 versus 28.9%) in the immunonutrition group [30]. Therefore there is sound evidence that nutrition and probably immunonutrition in certain circumstances can reach clinical goals and minimize complications.

**Is Nutrition Therapy Cost-Effective?**

In times when cost containment is one of the most important concerns for hospital administrators, a cost analysis may conclude that NT is an added cost of questionable benefit with low potential for increasing hospital revenue. However, it was shown that in an urban teaching hospital the 56% of patients at risk of malnutrition accounted for 72.5% of the total charges [15]. Malnourished patients, or those at risk of malnutrition, become a logical target for cost containment.

There are several ways to estimate cost-benefit and cost-effectiveness available. Risk-benefit analysis compares the morbidity and mortality due to the proposed treatment with the reductions in morbidity and mortality
that result from the treatment. Inherent complications associated with TPN and EN are well known. Their prevention can be achieved, thanks to strict procedure protocols, quality-control policies and a multidisciplinary nutritional team approach. These are low-risk, low-cost, very reproducible and controlled procedures. Benefits from NT are the lower costs derived by complications and savings due to shorter hospital stays. A cost-benefit analysis, expressed in monetary units, relates the monetary cost of a treatment to the value of the benefits produced. A cost-effectiveness analysis chooses the benefit to be achieved by a treatment and compares the monetary cost of different strategies to achieve it. A cost-analysis in NT suffers the bias that finding the true cost is very difficult. Economic cost (value of resources consumed) and charges (bill asking for payment) are completely different. Considering TPN, for instance, after the price paid to the vendor for the amino acids and glucose solution, there are charges for additives and equipment for mixing, pharmacy charges, and also overhead charges (depreciation of space and equipment, administrative costs, future expansion, etc.). It should be noted that a recent study has shown the possibility of reduction, when comparing different compounding systems. The ready-to-use compartmental bag required less application and manpower cost as well as pharmacy overhead cost [31]. Complications related to NT may jeopardize clinical results and have an impact on cost. A Spanish, noninterventional, ICU study, followed up 400 patients receiving EN. EN-related gastrointestinal complications were 62.8% and associated with longer length of stay and higher mortality [32].

Nutritional support teams were shown to decrease the cost of TPN and EN therapy by implementing appropriate protocols for delivering and monitoring NT. Unfortunately, in order to cut personnel costs some nutritional support groups were terminated. However, a retrospective review of 1,093 TPN patients in a tertiary care community hospital has verified that the reinstatement of the nutrition support nurse resulted in a decrease in costs of between USD 34,485 and 156,654. It was concluded that adequate staffing of a nutrition support team reduced inappropriate TPN and complications [33]. There are also intangible costs (discomfort, immobility, psychological dependency) and benefits (better quality of life) that should be considered, but again these are difficult to evaluate for NT. Still, it seems very hard to identify other strategies that could properly replace NT.

The provision of early NT was shown to reduce ALOS in a variety of clinical situations (Table 1).

The potential benefit of NT was shown in the Malnutrition Cost Survey study that evaluated nutritional risk, nutrition intervention, and length of hospital stay in 2,485 surviving adult patients from 20 acute medical and surgical bed hospitals in USA [8]. Nutrition intervention occurred when any form of NT met 60% of patient’s caloric requirement. The patient data were
divided into those without or with NT (32%). In half of the patients, NT was started up to the 3rd hospital day (early NT). ALOS for late NT was 3 days longer \((p < 0.001)\). In a selected group of 503 patients who stayed in the hospital from 8 to 40 days and were moderately at risk of malnutrition, a stepwise regression equation model focused on the length of hospital stay after the nutritional intervention as the outcome measure. Factors analyzed were: total diagnoses, day of nutritional intervention, expected ALOS, sex, surgery, height, age, and weight. The length in days of nutritional intervention, which was the only controllable factor, accounted for 19% of the total variation in post-nutritional intervention days. After rigorous statistical analysis, it was verified that for each 2 days of earlier intervention, there was a decline of 1 day in ALOS for the patients who received intervention (Fig. 3). Early NT patients stayed on average 2.1 days less than those given late NT. This amounted to a potential saving of 11.9 patient days/bed, or an average annual cost saving of USD 8,294/bed [34].

The Brazilian Society of Parenteral and Enteral Nutrition organized a theoretical economic study, in order to verify the cost impact of nutritional interventions in the city of São Paulo’s health care system. Considering the total health actions, the expenses with parenteral nutrition and EN constitute 0.14% of the total health care costs and just 0.33% of the whole hospitalization costs. The theoretical need to increase 302.2% in the nutritional intervention costs would not affect the total cost, if the hospital average ALOS were reduced by just 1%, corresponding to a 79-min average time reduction [35]. This economic study showed that for each BRL 1 (national currency, approximately USD 0.60 in September 1999) invested in nutritional interventions, BRL 4.13 would be saved in total health care costs.

**Fig. 3.** Cascade of cost-efficiency and cost-benefit in nutritional intervention.
The use of immunonutrition in critically ill patients was associated with a reduction in the length of stay in the ICU by 2.9 days, which could result in significant financially savings [29].

A PRCT held in Italy calculated the costs of postoperative complications and evaluated whether the use of preoperative enteral immunonutrition could lead to a saving in health care resources consumed [36]. EN was given to 206 patients and the specificity of enteral immunonutrition versus a standard enteral diet was evaluated according to the possible cost reflex. Estimates of costs were based on resource use for treatment of complications, which were valued according to the National List of Sanitary Costs of the Italian Ministry of Health and on the medical Diagnosis-Related-Group (DRG) reimbursement rates. Costs of nutrition were calculated and cost comparison and cost-effectiveness analyses were carried out. Intent-to-treat analysis showed that the total costs of the 52 postoperative complications that occurred were EUR 322,218, with a consumption of the DRG reimbursement rate of 15.4%. The costs of nutrition, the total costs (nutrition plus treating complications), the mean total costs per patient were lower in the treatment group. In conclusion, the cost-effectiveness analysis showed a net saving of EUR 2,386/complication-free patient in favor of the treatment group. Therefore, the perioperative use of immunonutrition appears cost-effective, due to a substantial saving of resources used to treat postoperative complications.

The road to cost adequacy must pass through carefully chosen nutritional intervention to avoid the highly expensive loops of infection, sepsis and complications.

![Fig. 4. Influence of earlier nutritional intervention on length of stay. From Miguel [34].](image-url)
In order to obtain the best clinical results, cost results and patient results, it is mandatory to follow strict protocols and to practice appropriate NT. This will help to decrease death, disease, disability, discomfort and dissatisfaction of our patients and favor better quality of life. To obtain these positive results, it is of interest to follow the cascade of cost-efficiency and cost-benefit in nutritional intervention depicted in Figure 4.

**Conclusion**

Hospital malnutrition is universal and highly prevalent. Higher morbidity, mortality, length of hospital stay and health care costs are associated with hospital malnutrition.

A significant reduction in major complications was observed in malnourished patients treated with nutritional support. This should prompt physicians to redouble their efforts to stratify their patients into those who are malnourished and those who are well nourished and thereby identify that large segment of the patient population who will truly benefit from the use of NT.

NT is a complex procedure requiring a multidisciplinary health care effort to be implemented safely. The best nutritional strategy should be chosen for each patient with the use of the digestive tract whenever possible. NT-related complications may jeopardize the possible benefits, particularly in critically ill patients. Nutritional policies and protocols should be implemented in order to obtain the maximum NT efficacy and reduce costs based on clinical evidence.

Improvment in the nutritional knowledge of health care practitioners and their capacity to identify malnutrition, as well the hospital screening programs for nutritional risk, are mandatory and should be regarded as a long-term investment by health care management.

With these premises fulfilled, NT is cost-beneficial and cost-effective.

**References**

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Discussion

Dr. Griffiths: I noticed that in your Brazilian study you had a 10% incidence of malnutrition and an 11% incidence of nutritional therapy. Were those cohorts well-matched? In other words, how many of the 10% malnourished population were receiving nutritional therapy, or was the 11% nutritional therapy being targeted to the wrong sector of the population?

Dr. Waitzberg: This study was a cohort study, so the patients were looked at in various settings in different hospitals. What we know is that there is around 13% of severe malnutrition, and almost 37% of moderate malnutrition. We also looked at a range of nutritional variables, where they were available, and I should say that what we considered to be moderate malnutrition would be considered severe malnutrition in Europe and the USA. Our cases of severe malnutrition had lost more than 25% of their
body weight. So we believe we are justified in thinking that there was underprescription of nutritional therapy.

**Dr. Griffiths:** Also, I noticed that when you were looking at the covariables that described morbidity and mortality, infection was only a covariable for morbidity and was actually lost in the relation linking malnutrition and mortality. I am puzzled that infection does not appear to be a variable that predicts mortality in your malnourished population.

**Dr. Waitzberg:** When we analyzed the entire population of 4,000 patients, then infection was a significant cofactor, along with cancer and being over 60 years old.

**Dr. Labadarios:** You showed us data on cost of enteral nutrition vs. mortality. Why did you do that analysis?

**Dr. Waitzberg:** We were alarmed by the huge amount of malnutrition that we uncovered, so we decided that we had an obligation to ask the government to pay for enteral nutrition. In order to do this we felt that it was insufficient only to show the malnutrition data, so we asked help from economists to do a theoretical study. This was done using our databank and was statistically very powerful; it has already been published in a Brazilian journal [1]. With this information, we managed to persuade the government to change the law to include nutritional therapy, as required, for every public patient in Brazil, at a cost of around USD 15–18/day. This is an important concept: when we discuss costs with hospital administrators, they only consider them in the short term in relation to their budgets. In our analyses, we considered the total integrated cost to the health service, which included all the variables.

**Dr. Mokgokong:** I am most confused. You told us that immunomodulation will reduce the infection rate, reduce days of ventilation, and reduce hospital stay, and yet you ended up by saying there was no change in mortality! Why? Is there just a postponement of death? Where do these patients die? Do they die in the hospital, outside the intensive care unit, or after being discharged home?

**Dr. Waitzberg:** This is a very difficult question. Would you like to comment Dr. Griffiths?

**Dr. Griffiths:** I think you have hit on an important point which I was trying to get over earlier: meta-analysis muddles up populations that have a high risk of mortality, where you can indeed look at mortality as a variable, and populations where there is little or no risk of mortality, where mortality is not therefore a reliable variable to be examined. In those populations where there is no mortality – that is, elective surgical patients undergoing routine elective surgery – dietary therapy can reduce the length of stay and reduce the infective morbidity, and that is where the studies have shown the benefits. So when you do a meta-analysis in patients who have no risk of mortality, you find a reduced length of stay and a reduced infective morbidity but you won’t find an effect on mortality, because these are not populations in which mortality has a very high risk of occurrence in the first place.

**Dr. Mokgokong:** Yes, but can we take it a little further and examine what happens in patients who do have a risk of mortality? Why is nutrition support not ultimately ending up with an improvement in mortality?

**Dr. Waitzberg:** I would like to give another point of view. Some years ago in the 1980s, papers started to appear saying that nutritional support was not changing mortality in cancer. I remember one expert saying ‘who says that nutritional support is entitled to change mortality in cancer? What changes mortality in cancer is surgery, radiotherapy, chemotherapy, and so on, if anything.’ I think this issue remains the same – are we addressing the right question? Should we expect nutrition to change mortality in a complex situation, where you have hypoxia, acidosis, infection, and so on?

**Dr. Griffiths:** It is my fault that I did not make this issue clear enough in my talk. If you are looking at a deficiency state, which is what malnutrition is, you can hope
to affect an outcome such as mortality. But in the immunonutrient work, it is only in the glutamine studies, or rather only in the parenteral glutamine studies, where you can truly say you are looking at a deficiency, and therefore that supplementation is reversing a deficiency state. The other immunonutrient studies are different; they are not based on the principle of a deficiency, they are based on trying to alter a pathophysiological process. The argument may be valid and it has been shown to be valid in the less sick group of patients, but in the sicker patients I think we just don’t know the answer.

Dr. Labadarios: I want to make a point for perspective. I think it is a relevant question to ask what we are trying to prove, against the background of the knowledge we have. We know that starvation kills, there is no doubt about that; we don’t need trials to prove it. We also know that starvation kills more rapidly in the presence of catabolic illness. So we need to maintain the perspective, even though this may be thought of as a philosophical viewpoint, or even a cynical viewpoint. But we must have a perspective in terms of what we are trying to prove, within the complexities of the situation. Coming to Dr. Griffith’s point, I fully understand what he says, but I would say that his view is only one possible explanation. There may be another way of looking at this. Is it possible that, because of our frequent lack of understanding of the pathophysiology of the conditions we are dealing with, and their multifactorial nature, we are actually doing harm? For instance we have just finished a study in Mozambique on cerebral malaria, where we thought that vitamin A could be beneficial. It was indeed marginally beneficial, but the survivors had neurological deficits, so one wonders about the appropriateness of the intervention. We also have evidence that vitamin A supplementation in the presence of respiratory infections increases morbidity. These are two examples that are documented in the literature. So one wonders whether we fully understand the possibility that there may be other mechanisms, whereby mortality is increased in these patients.

I would like to ask Dr. Griffiths what does he do in his unit, whom does he feed, how he feeds his patients, and whether he uses any of the special immunonutrition enteral diets. I ask that because of the title of the workshop (‘early intervention’), and because I wasn’t given the chance to ask the question when Dr. Griffiths spoke. I hope Dr. Waitzberg will pardon this intrusion on his question time, but it is relevant to his subject as well.

Dr. Griffiths: Well, I follow very traditional views, so if you take 100 admissions there will probably be about 40–50 who don’t have any nutrition at all, because they are in rapid passage – severe asthmatics and so on – so we are left with about 50% of our patients who are going to require some form of nutritional support. Of these remaining patients, only about 6–7% in a general intensive treatment unit will have severe pathologies such as gut failure that prevent them from having enteral nutrition. These patients will have undergone resuscitation, so it will usually be a day or so before they actually start having a parenteral nutrition regimen. The urgency will depend on our clinical assessment of how malnourished they are, so we will be more aggressive in starting our parenteral nutrition regimen in the most undernourished patients. Those patients who are going to receive parenteral nutrition will have what I believe to be a more correctly formulated regimen than is normally given, in that it has glutamine in it. My study was about that small population of intensive treatment unit patients specifically. There is going to be a larger group of patients who will start to be fed at a time determined by our assessment of whether they are ready for it. This will be an enteral process, not a parenteral one, and only patients we start within the first 24–36 hrs will be those who are clearly not infected. So somebody who has had trauma and in whom we are confident there is no intra-abdominal lesion by the nature of the
history, or those with burns injuries, can be started on a standard polymeric enteral feed within a few hours.

In patients with pneumonia we will very slowly start some nasogastric feeding, when we feel we are getting on top of things clinically.

If we have trouble with gastric emptying, then we will consider inserting a nasojugal feeding tube at that point.

Does that answer the question?

Dr. Labadarios: Thank you, you made it perfectly clear, though you didn’t answer my point about direct mechanisms, whereby mortality could be increased!

Dr. Soeters: To follow up on the original question about why we cannot show efficacy with respect to mortality, there are several possible reasons. One is that mortality is multifactorial. Another is that those patients who benefit from parenteral or enteral nutritional support in intensive care units are mostly not included in the studies, because you cannot have a nontreatment arm. Ethics committees won’t accept deliberate starvation of a patient who is on a respirator for 4–6 weeks, so all of them get nutrition. If all of them get nutrition, you can only study the effect of modulation of nutrition, and if you have already given some form of nutrition, then most of the effects will already have been achieved.

Dr. Griffiths: That is exactly right. My study could merely have been a test of a nasty noxious parenteral nutrition compared with something slightly less nasty and noxious.

Ms. Marino: Could Dr. Waitzberg tell us what procedures or policies he has put in place since the identification of the high incidence of malnutrition, which we could perhaps take back to our own hospitals?

Dr. Waitzberg: A few things have been changed completely in Brazil after the results of the study. There is now a regulation from the Health Ministry insisting on a nutritional assessment of all patients in hospital. Secondly, you cannot give parenteral or enteral nutrition in any hospital in the country, unless you have a nutritional support team. Thirdly, you cannot give parenteral nutrition, unless you have a certified pharmacy, and all total parenteral nutrition (TPN) preparations must be formulated by pharmacists and no longer by nurses. Fourth, if you decide to use a noncommercial diet, you must provide a special room dedicated to enteral feed preparation, like a lactarium, and this must be supervised to ensure hygiene and regularly inspected by an appropriate agency. Many dieticians, nurses, and even pharmacists are now retraining themselves to adapt to this new situation.

Dr. Mwambo: We haven’t discussed the issue of HIV at all. In southern Africa, HIV is the most important problem we have, and the commonest cause of morbidity, hospital admission, and mortality. One of the most frequent reasons for admission of AIDS patients to hospital is infection, and there is always the co-morbid issue of malnutrition in the African setting. Could you comment on the dietary issues involved, and whether nutritional therapy would be cost-effective?

Dr. Waitzberg: The approach to malnutrition in HIV depends on the stage of the illness. Some patients come to hospital already malnourished and with severe secondary infections – that is, the advanced stage of AIDS. We have done a study on those patients using parenteral and even enteral nutrition, but unfortunately we have not had much success in improving their nutritional status when they reach this late phase of the disease. Then there are the patients who are HIV positive, but do not yet have the full spectrum of AIDS. These patients may be eating less than normal, and it is a good idea to give them oral supplements and to involve dieticians in their care. Finally, in countries where the new drug cocktails are readily available, we are seeing much less malnutrition in AIDS, but on the other hand we are now having problems with lipodystrophy and other changes in body composition related to the
drug treatment. So in summary, one’s aim should be to intervene early with nutrition support in AIDS patients, before they present with advanced disease, particularly if drug cocktails are not available.

Dr. Segal: AIDS is the overwhelming problem here, and unfortunately treatment is a politically loaded question at present. Our only real hope is early intervention with regard to nutrition. Besides that, most of the patients who present a gastrointestinal unit are patients with upper gastrointestinal tract candida with dysphagia, or with diarrhea. Early intervention is fine, but can we be more specific? Should we be looking at CD4 counts and so on to decide on the right time for intervention? Bearing in mind the costs and the patient load, TPN is certainly not practical.

I think this is a very important issue and we would greatly appreciate it, if we could have guidelines on clinical nutrition in AIDS patients.

Dr. Waitzberg: I can give my view, and I’m sure that Dr. Pichard, who is an expert in HIV, will give his as well. Some years ago, the task force on AIDS in the USA produced some guidelines about nutrition in AIDS [2]: ‘early nutrition’ involved oral nutrition with added vitamins E, A, C, and B1, and an increase in the energy and protein offered to these patients. As far as I remember, this was to be instituted as soon as the diagnosis was made without waiting for the decrease of CD4/CD8 ratio. It was recommended that patients should have a nutrition assessment to see what they were eating, and it is assumed that energy expenditure would have been increased by at least by 30%. Parenteral nutrition would seem to be of limited value in cases of advanced AIDS. Do you have any data on this, Dr. Pichard?

Dr. Pichard: I am very sad about the HIV epidemic in Africa but more specifically in South Africa. I don’t have any ready solution, but I can share our experiences in the Geneva University Hospital, which is a 2,000-bed hospital which at one time, in the 1980s, had more than 100 beds occupied by advanced cases of AIDS. At that time, a substantial proportion of our resources, in terms of manpower and nutritional support techniques, was being used to try to feed advanced stage AIDS patients. The results were extremely depressing. Oral feeding had virtually no impact. Enteral nutrition was of limited value, because most patients were unable to tolerate more than 1,000 kcal/day given as a continuous infusion; if it was increased above that level, they developed severe diarrhea, with up to 15–20 bowel motions in 24 hrs. When we used parenteral nutrition, we had an ‘epidemic’ of severe catheter-related infections.

My feeling now, as a result of that experience, is that without the effective drug treatments that are now available, any financial investment that is made to help these patients is going to be a waste of money. Maybe it will be useful in terms of human compassion, but not in any other way. I am afraid that what you need is access to efficient drug therapy. Then you will find that at least a third of patients will not need any nutritional support at all, one third may need help occasionally, and only the final third really needs some kind of continued nutritional support. This is what we have experienced during the last about 15 years, and I can only hope that you will have access to efficient drugs in the near future.

Dr. Waitzberg: I completely agree.

Dr. Mokgokong: There is no point us being very emotional about these things. When you talk of effective drug therapy against AIDS, you’ve got to define what you are talking about. You are dealing with a situation where the body is trying to fight infection, so in the acute stage surely the state of the body’s immune defense mechanisms is very important. We see a lot of these patients, and many of them die. But by looking after them well, giving them proper nutrition, and treating opportunistic infection, we find that patients who come in moribund can recover sufficiently to walk out of hospital. So I don’t go along with the view that there is nothing we can do without drug therapy – that’s too emotional a viewpoint. In my view, treating opportunistic
Infections adequately in the acute stage is more important than treating the virus itself. That is my opinion from the experience we have in this country.

Dr. Waitzberg: Well, let’s imagine that you have AIDS and also no possibility of buying food. Then you have two different diseases – AIDS infection and malnutrition associated with poverty, with the attendant anorexia. Of course if you give protein and calories under those circumstances, one of the problems will be resolved. However, in our own experience with hospitalized advanced AIDS patients the benefits of nutritional therapy were marginal [3]. On the other side there are reports of beneficial body composition changes with aggressive nutrition [4]. Maybe those studies should be revisited.

Ms. Marino: You have picked up on a very important point. We attend many erudite lectures on nutrition and AIDS, but if people haven’t got the money to buy food nothing else will be of any use. The big issue is to alleviate poverty.

Dr. Waitzberg: I feel comfortable talking about this subject, because we have much poverty and malnutrition in my country too. In my institution – in the University of São Paulo – we developed a program for giving enteral nutrition orally or by tube to patients who don’t have the resources to buy it. This program has already existed for 10 years and it has proven to be very cost-effective. Surgical patients, for example, are given enteral feeding for 7–10 days at home before returning to the hospital for their operations.

References