

# Protein-Energy Malnutrition in Hospitalized Patients: Early Assessment for Better Outcome

Yishai Levy MD

Department of Medicine D, Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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The 20th century was characterized by major developments in nutrition science and practice: deficiency syndromes of macro- and micro-nutrients were defined, the pathophysiological basis and clinical consequences of human starvation were investigated, and dietary requirements were formulated [1]. Until the 1970s it was thought that malnutrition was a phenomenon that existed exclusively in developing countries and in areas of the world under crisis and economic instability. Later it became apparent that the problem of malnutrition existed also in hospitalized patients and in various disease states, in both medical and surgical patients, in different countries [2,3].

In general, malnutrition is used to describe a wide spectrum of conditions with an imbalance between intake and requirements, ranging from under-nutrition to over-nutrition. Usually, under-nutrition follows reduced food intake, increased body requirements, malabsorption syndromes, or any combination of such states. ESPEN, the European Society for Clinical Nutrition and Metabolism (formerly the European Society of Parenteral and Enteral Nutrition) presented a consensus document that contained an adapted definition of malnutrition that distinguishes between cachexia, sarcopenia (loss of muscle mass and function) and malnutri-

tion [4]. Whereas cachexia is always an expression of a disease accompanied by enormous changes in body composition with a grave prognosis due to increased and progressive protein catabolism, hospital malnutrition may result from poor intake due to reversible etiologies, such as acute infection, low food availability, and depression. This is in contrast to chronic wasting diseases with a poor prognosis, such as advanced dementia or any severe organ failure.

A recent international consensus committee has proposed revised definitions of malnutrition [5]. “Starvation-related malnutrition” develops in cases of chronic starvation without inflammation, “chronic disease-related malnutrition” is diagnosed in cases with mild to moderate degrees of inflammation, and “acute disease- or injury-related malnutrition” occurs when inflammation is acute and of severe degree. This stratification highlights the emerging role of pro-inflammatory cytokines that mediate complicated starvation. Such definitions are in line with the traditional historical types of protein-energy malnutrition, namely – marasmus, which is due to low energy intake over a prolonged period and has a relatively benign clinical course, and kwashiorkor, which is characterized by an acute disease course due to low protein and energy resources [6]. Whereas marasmus leads mainly to fat deposit depletion, kwashiorkor or protein-energy malnutrition with stress-associated malnutrition leads to accelerated depletion of muscle and visceral organs with ensuing high mortality rates.

Numerous studies have demonstrated the extent of malnutrition in hospitals, with a prevalence reaching 50% depend-

ing on the patient population and the criteria of malnutrition [7]. For instance, a British study that is frequently cited on the subject investigated 500 patients in an acute-care teaching hospital in Dundee, Scotland. An underweight prevalence of 40% (body mass index < 20 kg/m<sup>2</sup>) was observed with a 5.4% further weight loss in 112 patients reassessed on discharge. Under-nutrition was not recognized during the hospital stay in most of these patients [8]. The German Hospital Malnutrition Study diagnosed malnutrition in 27.4% of 1886 patients admitted to private and university hospitals [9]. Malnutrition was present in 48.1% of 4000 patients in hospitals in Brazil, but only 18.8% of patients’ records provided any nutrition-related information [10]. A Danish study screened 750 patients and found that 22% were at risk for malnutrition, while dietary plans and records were missing in the majority of these patients [11]. To complete the wide geographic distribution of studies, a recent review has illustrated the extent and implications of malnutrition in the Australian health system [7].

Nutrition assessment comprises a history-taking, and physical, clinical, biochemical and anthropometric evaluation. Numerous scoring systems for nutritional screening have been developed. The longest in use is the SGA (Subjective Global Assessment), which looks at 10 items – 5 in patient history and 5 in physical examination – ranking them as well nourished, moderate nutrition and severe malnutrition [12]. The MUST (Malnutrition Universal Screening) was developed in the UK and utilized BMI, unintentional

BMI = body mass index

weight loss and acute disease effect. This scoring system has a high predictive value for mortality and length of stay rates [13]. NRS 2002 (Nutrition Risk Screening) was developed by ESPEN for use primarily in Europe. This easy-to-use system gives a score for impaired nutritional status and severity of disease, taking into consideration advanced age [14]. These are three of the most practiced assessment tools, which are primarily oriented toward identification of patients requiring special nutritional care in and out of the hospital.

Many years after the first reports, it was appropriate for Israeli hospitals to join the initiative against the “hidden malnutrition,” rightfully described as “the skeleton in the hospital closet.” Indeed, Israeli hospitals participated in the nutrition screening and risk assessment “nutritionDay” study: this was a one day screening program with one month follow-up in 2007/2008 of 21,007 patients in 1217 units of 325 hospitals in 25 countries across Europe and Israel [15]. Nutrition risk was evident in 27% of patients; these patients were older and had lower BMI and pronounced loss of weight, and 43% of patients did not reach energy goals of 1500 kcal daily. Notably, different screening tools were used with the NRS 2002 more than with the MUST system. Huge differences were observed between hospital units and countries. An Israeli study that used the MUST system was published recently. It followed 1000 patients with a mean age of 67.6 years admitted to a single internal medicine department. High risk for malnutrition was identified in 25.4% of the patients. Such a risk was associated with prolonged hospital stay and an increase in mortality rate [16]. It is timely, therefore, and instructive to note the complementary information from a study published in the present issue of *IMAJ* [17]. Giryas et al. used the NRS 2002 for screening adult patients admitted to all hospital departments (except emergency and maternity) during a 5 week period. Among 504 patients, 31.5% were defined as high risk.

The prevalence in the internal medicine department was twice that in the surgery department. Nutrition risk was associated with significant older age. Worth mentioning is the strict methodological design that used self-reporting and validated anthropometric measurements and equations in cases where directly measured height and weight were not possible, underscoring the feasibility of obtaining information in bedridden and very sick patients.

The prognostic implications of malnutrition were extensively reviewed by Norman et al. [18] in 2006. Increased mortality and morbidity, poor wound healing, infectious complications and slow recovery were all related to malnutrition. Altogether, hospital stay was extremely prolonged with a consequent increase in treatment costs and real impairment in quality of life.

Early recognition of malnutrition is crucial for any management that should be followed by different nutrition support techniques. Food supplements and enteral nutrition by nasal or gastrostomy routes are often provided. Parenteral nutrition is exceptionally ordered in specific cases where the gastrointestinal tract is non-functional or obstructed. Understandably, assessment of the patient is the first step in any such nutrition support regimen.

The two Israeli studies sound the alarm: although two different scoring systems were used, comparable results were recorded. Both studies show a significant risk of malnutrition in a quarter to one-third of patients newly admitted to Israeli hospitals, similar to the rest of the world. Though often not utilized, screening must be incorporated in high quality protocols for patient care. Furthermore, it is anticipated that nutrition support may improve clinical outcome and quality of life in patients at nutritional risk [19,20].

In conclusion, we strongly stand behind the authors' concluding remarks that “in addition to its devastating effects on patients, malnutrition impacts significantly on the health care system.”

The development of a comprehensive nutrition care protocol in the framework of the hospital accreditation process is a reasonable request based on the Israeli experience [17,18].

#### Corresponding author:

**Dr. Y. Levy**

Dept. of Internal Medicine D, Rambam Health Care

Campus, Haifa 31096, Israel

**Phone:** (972-4) 854-2263

**Fax:** (972-4) 854-3286

**email:** ys\_levy@rambam.health.gov.il

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**Capsule**

**Restoration of vision after transplantation of photoreceptors**

Cell transplantation is a potential strategy for treating blindness caused by the loss of photoreceptors. Although transplanted rod-precursor cells are able to migrate into the adult retina and differentiate to acquire the specialized morphological features of mature photoreceptor cells, the fundamental question remains whether transplantation of photoreceptor cells can actually improve vision. Pearson et al. provide evidence of functional rod-mediated vision after photoreceptor transplantation in adult *Gnat1*<sup>-/-</sup> mice, which lack rod function and are a model of congenital stationary night blindness. The authors show that transplanted rod precursors form classic triad synaptic connections with second-order bipolar and horizontal cells in the recipient

retina. The newly integrated photoreceptor cells are light-responsive with dim-flash kinetics similar to adult wild-type photoreceptors. By using intrinsic imaging under scotopic conditions they demonstrate that visual signals generated by transplanted rods are projected to higher visual areas, including V1. Moreover, these cells are capable of driving optokinetic head tracking and visually guided behavior in the *Gnat1*<sup>-/-</sup> mouse under scotopic conditions. Together, these results demonstrate the feasibility of photoreceptor transplantation as a therapeutic strategy for restoring vision after retinal degeneration.

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**Capsule**

**Prions also interact with components of the miRNA pathway**

MicroRNAs (miRNAs) are small non-coding RNAs that, when part of a miRNA-induced silencing complex (miRISC), repress the expression of fully or partially complementary mRNAs. Argonaute (Ago) proteins bind miRNAs and form the heart of the silencing machinery. Intriguingly, plasma membrane-associated forms of the human prion protein (PrP<sup>C</sup>), which is associated with neurodegenerative diseases in humans, also interact with components of the miRNA pathway. Gibbings et al. show that a transmembrane form of PrP<sup>C</sup> exposes an AGO anchor sequence in the cytoplasm and that this repeat binds AGO1 and AGO2. These PrP<sup>C</sup>-AGO complexes are found on vesicles in cells that resemble multivesicular bodies (MVBs). During miRNA maturation, AGO protein bound to miRNA

must be transferred from the RISC-loading complex (RLC) to the miRISC-silencing complex. PrP<sup>C</sup> binds components of both the RLC and the miRISC but seems to do so in distinct cellular locations. PrP<sup>C</sup> promotes the association of AGO with the miRISC and/or the stability of this complex. Indeed, PrP<sup>C</sup> is required for effective miRNA silencing of a number of target mRNAs. PrP<sup>C</sup> may do this through subcellular trafficking, as it seems to increase the interaction between MVBs and AGO-rich structures, such as P or GW bodies, thereby promoting shuttling of AGO between the RISC-loading complex and the miRNA-induced silencing complex.

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Eitan Israeli

**In everyone's life, at some time, our inner fire goes out. It is then burst into flame by an encounter with another human being. We should all be thankful for those people who rekindle the inner spirit**

Albert Schweitzer (1875-1965), German theologian, organist, philosopher, physician and medical missionary. He received the 1952 Nobel Peace Prize for his philosophy of "Reverence for Life," expressed in the founding and sustaining of the Albert Schweitzer Hospital in Lambaréné, Gabon

# *Haemophilus influenzae*: Still a Relevant Invasive Pathogen

Shalom Ben Shimol MD and Ron Dagan MD

Pediatric Infectious Disease Unit, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel

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**H***aemophilus influenzae* is a small, non-motile, gram-negative pleomorphic coccobacillus, generally considered a constituent of the upper respiratory tract normal flora of humans [1]. Strains without polysaccharide capsules (non-typable *H. influenzae*) often cause mucosal surface infections, while encapsulated strains, especially *H. influenzae* type b, cause invasive diseases such as septicemia and meningitis [1]. Prior to the universal introduction of Hib vaccines, Hib was a common cause of bacterial meningitis, epiglottitis and sepsis in children worldwide, including Israel [1-4]. Thus, prevention of invasive Hib disease through immunization is considered one of the greatest public health achievements of the late twentieth century [2]. Furthermore, conjugate Hib vaccine administration reduces Hib carriage, resulting in reduced transmission and thus indirect protection (herd protection) [5].

Routine vaccination with Hib conjugate vaccines was introduced in the United States in 1987-1990 [1,6]. Since January 1994, all infants in Israel are offered Hib conjugate vaccine free of charge as part of the universal national immunization plan [5]. This has resulted in a rapid and remarkable decrease in the incidence of invasive disease in all settings where the vaccines have been incorporated into routine infant immunization schedules [5-7]. In Israel, the incidence of

Hib disease in children under the age of 5 years dropped from 34 per 100,000 before the licensure of Hib conjugate vaccines to 4 per 100,000 in 1995 and 2 per 100,000 in 1996 [5]. This > 90% reduction was similar to that observed in other developed countries [6,8,9].

It has been estimated that Hib vaccines prevent annually 21,000 cases of Hib meningitis and ~38,000 cases of invasive Hib disease [10]. The impact of Hib vaccination on the incidence of pneumonia is likely to be several-fold greater than the impact on meningitis, though demonstrating this impact is complicated because of the difficulty in establishing an etiologic diagnosis of pneumonia [11].

The development of invasive Hib disease after prior administration of a Hib conjugate vaccine (Hib vaccine failure) is uncommon but has been reported in other countries with established Hib vaccination programs, including those with routine booster doses in the second year of life [8]. It has been suggested that children with Hib vaccine failure are inherently unable to maintain long-term antibody-based immunity against Hib. Those children may be at risk of further episodes of invasive Hib disease [8]. Children with Hib vaccine failure had a higher incidence of immunoglobulin A deficiency than the general population, suggesting that an invasive Hib infection can be the first clinical sign of common variable immunodeficiency [12]. However, in a study from Israel of five fully immunized patients with invasive Hib infections, immunologic studies were carried out in four and only one patient exhibited mild IgG2 deficiency [5].

The near-elimination of Hib disease in some populations led to the speculation that other *H. influenzae* serotypes

(especially serotype a) and NTHi may emerge as important causes of invasive disease [7,13]. Other concerns were raised regarding the possibility of replacement by non-*Haemophilus* pathogens (e.g., *Streptococcus pneumoniae* and *Neisseria meningitidis*) [14]. Previous results from Israel did not support the replacement theory in children [5]. However, recent reports from various countries describe an increase of non-b *H. influenzae* invasive disease in adults > 65 years old, including disease caused by NTHi [15]. In the post-Hib vaccine era, the majority of cases with the disease are caused by NTHi in all age groups, with a higher incidence among adults > 65 years old than among other age groups [6,15].

In high risk populations, the clinical characteristics of NTHi invasive disease among children are similar to those of Hib disease: meningitis is the most common presentation and the majority of children with meningitis are < 1 year of age [13]. Vaccines for the prevention of non-type b *H. influenzae* infections are not currently available [7].

Additional studies are needed to advance our understanding of the microbial milieu of the mucosa and to assess the "ecological impact" of conjugate vaccines. Although vaccination with Hib conjugate vaccines does not appear to increase the risk of colonization with non-type b *H. influenzae*, there are few data on the effect of other vaccines. The relationship between *S. pneumoniae* and *Staphylococcus aureus* colonization is illustrative. A cross-sectional study from Israel demonstrated lower rates of nasal colonization with *S. aureus* among children who were colonized with *S. pneumoniae* serotypes included in the conjugate vaccine [16].

Hib = *H. influenzae* type b

IgG = immunoglobulin G

NTHi = non-typable *H. influenzae*