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Prof. Philipp Schuetz, MD[1,2], Prof. David Seres, MD[3], Prof. Dileep N. Lobo, FRCS[4,5], Filomena Gomes, PhD[6,7], Nina Kaegi-Braun, MD[8], Prof. Zeno Stanga, MD[9]

1) Medical University Department, Division of General Internal and Emergency Medicine, Kantonsspital Aarau, Aarau, Switzerland,
2) University of Basel, Switzerland,
3) Institute of Human Nutrition and Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA
4) Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Queen's Medical Centre, Nottingham, UK
5) MRC Versus Arthritis Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, UK
6) The New York Academy of Sciences, New York City, NY, USA
7) NOVA Medical School, Universidade NOVA de Lisboa, Lisboa, Portugal
8) Division of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Kantonsspital Aarau, Aarau, Switzerland,
9) Division of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

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Correspondence and reprint requests:
Prof Dr med. Philipp Schuetz, MD, MPH
University Department of Medicine
Kantonsspital Aarau
Tellstrasse, CH-5001 Aarau, Switzerland
Tel: +41 62 838 4141(phone), Fax: +41 62 838 4100
Email: schuetzph@gmail.com

Summary

Disease-related malnutrition in adult patients who have been admitted to hospital is a syndrome associated with substantially increased morbidity, disability, short-term and long-term mortality, impaired recovery from illness, and cost of care. There is uncertainty regarding optimal diagnostic criteria, definitions for malnutrition, and how to identify patients who would benefit from nutritional intervention. Malnutrition has become the focus of research aimed at translating current knowledge of its pathophysiology into improved diagnosis and treatment. Researchers are particularly interested in developing nutritional interventions that reverse the negative effects of disease-related malnutrition in the hospital setting. High-quality randomised trials have provided evidence that nutritional therapy can reduce morbidity and other complications associated with malnutrition in some patients. Screening of patients for risk of malnutrition at hospital admission, followed by nutritional assessment and individualised nutritional interventions for malnourished patients, should become part of routine clinical care and multimodal treatment in hospitals worldwide.

Introduction

Malnutrition indiscriminately affects individuals at all stages of life, from infants and children to adolescents and older adults. According to WHO,[1] malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy or nutrients and includes three groups of conditions—namely, undernutrition (eg, wasting, stunting, and underweight), micronutrient-related malnutrition (eg, iron deficiency anaemia, vitamin A deficiency, and iodine deficiency disorders), and overweight (eg, obesity and non-communicable diseases that are diet related). Although undernutrition and micronutrient deficiencies were once associated with low-income and middle-income countries, and overnutrition with high-income countries, many parts of the world now have all of these malnutrition-related problems. With advances in medical treatment and the rising number of patients who are older than 65 years and have multiple morbidities, disease-related malnutrition in patients with multiple illnesses has become a growing concern.

Data from the USA and Europe show that up to a third of patients in hospital have malnutrition or are at risk of malnutrition at the time of hospital admission.[2-6] Additionally, a patient's nutritional status often deteriorates during their hospital stay due to illness-related loss of appetite, drug-related side-effects, fasting orders for diagnostic studies, diseases that impair the normal functioning of the digestive system, overall suboptimal management of inpatient nutrition, and disease-related and disuse-related wasting. Patients sometimes feel that poor appetite is to be expected during treatment in hospital and both patients and medical staff can believe that medical treatment is the main priority and that food is of secondary importance.[7]

Malnutrition has been historically defined as insufficient intake or uptake of nutrition that leads to altered body composition (loss of fat-free mass) and body-cell mass, which, in turn, causes decreased physical and mental function and impaired clinical outcome.[8] Yet, this definition of malnutrition is only one of several found in the literature, leaving considerable scope for confusion and misunderstanding.[9, 10] Disease-related malnutrition is a complex syndrome resulting from inadequate intake of nutrients that does not fulfil the patient's physiological requirement and from disease-related systemic inflammatory response. The absence of simple and unequivocal diagnostic criteria that have high specificity and sensitivity for malnutrition has been an obstacle to consensus. In addition, most diagnostic criteria for malnutrition were validated with regard to their use in predicting adverse clinical outcomes, such as morbidity and mortality, rather than predicting which patients might respond to nutritional therapy. Nevertheless, progress has been made in defining disease-related malnutrition and global experts have now proposed a framework to help in the diagnosis of malnutrition.[8] New diagnostic criteria for malnutrition, applied to patients who are medically or surgically unwell, include alterations in body composition that result from an inflammatory response.[11-14] Thus, the main drivers for disease-related malnutrition can be from inflammation-driven or undernutrition-driven catabolism.

There is a strong association between malnutrition and increased risk of adverse clinical outcomes, which include higher rates of morbidity and mortality, functional decline, and prolonged hospital stays.[3, 15] Associations between malnutrition and adverse clinical outcomes are largely independent of the underlying medical condition.[3, 5] We, and other researchers, have concluded that early recognition of malnutrition at hospital admission

through active nutritional screening, nutritional assessment, and adequate treatment are important elements of patient care in medical wards.[16] Fortunately, the specialty concerned with nutrition for inpatients with medical conditions has advanced substantially. Historically, evidence encouraging nutritional interventions was inadequate and relied mainly on observational research.[17] However, several trials studying the role of nutritional therapy for patients being treated in hospital have changed the understanding of the management of malnutrition and have identified malnutrition as an important target for intervention.[18] This Review provides an up-to-date view of current approaches to best identify and manage disease-related malnutrition in adult patients who are being treated for medical conditions (ie, not having surgical treatment) in the hospital setting. Approaches include patient screening for the risk of malnutrition at hospital admission, nutritional assessment and application of diagnostic criteria for malnutrition, evidence-based nutritional algorithms to provide best nutritional care for individual patients, selection of patients most likely to benefit from nutritional interventions, and nutritional considerations after discharge from hospital.

Search strategy and selection criteria

We searched MEDLINE with the terms "disease-related malnutrition", "malnutrition", and "malnourished", in combination with one or more of the terms "pathogenesis", "pathophysiology", "diagnosis", "screening", "assessment", "treatment", "nutrition(al) support", "nutrition(al) intervention", "hospital", and "inpatient", for articles published from Jan 1, 2011, to Jan 6, 2021. We identified the articles on adult medical inpatient populations and selected the most relevant clinical trials, systematic reviews, and high-quality review articles. Studies of critically ill or surgical patients were excluded. We also manually searched reference lists of identified articles to retrieve additional studies.

Pathogenesis

Malnutrition can result from one or a combination of the following factors: starvation, disease (eg, polypharmacy, disease-related inflammatory mechanisms, and compromised intake or assimilation of nutrients), immobility-associated muscle wasting,[19] and older age or social isolation.[20] Although the pathogenesis of disease-related malnutrition is complex in general, acute and chronic inflammation have been found to be key contributing factors to reduced appetite with a decrease in intake of energy and protein. Endocrine changes also lead to catabolism, fatigue, and immobilisation (figure 1).[21] Cytokines, such as IL (interleukin)-6 and tumour necrosis factor α (TNFα), affect brain circuits that control food intake, delay gastric emptying, and influence skeletal muscle catabolism. Acute and chronic illnesses also impact various endocrine systems, resulting in catabolism (eg, increase in cortisol concentrations, down-regulation of sex hormones, and peripheral growth hormone resistance). Cytokines modulate the hypothalamic–pituitary–adrenal axis response and stimulate the release of stress hormones, including cortisol and catecholamines, which, in turn, increase muscle catabolism.[22, 23] Incretin hormones (such as glucagon-like peptide-1 [GLP-1; pro-glucagon]), which are released directly from gut tissues, also affect malnutrition. There is evidence of interaction between inflammatory cytokines (mainly IL-6 and IL-1β) and GLP-1 (and its analogues) that resulted in reduced food intake and unintentional weight loss.[24] Finally, illness-related factors, such as gastrointestinal dysfunction, logistics of care,

and concerns about feed-related complications, such as aspiration for enteral nutrition and sepsis for parenteral nutrition, can lead to chronic underfeeding.[25] Patients admitted to hospital have the additional burden of acute illness, inflammation, immobilisation, and variability of standards of hospital food, all of which can contribute to malnutrition.

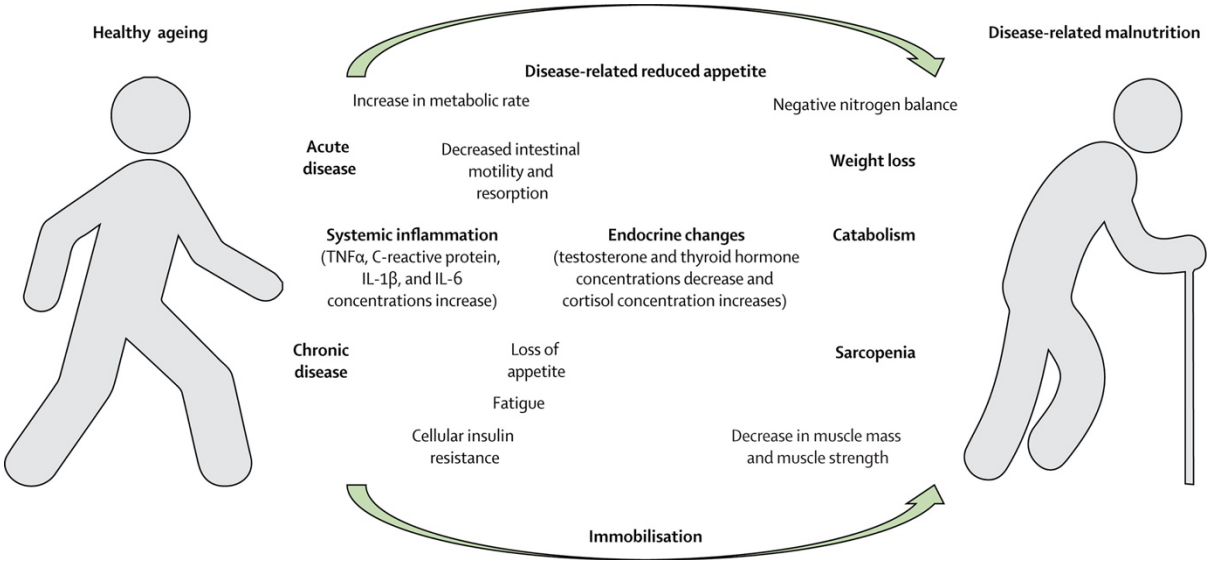

Figure 1. Pathophysiology of malnutrition
IL=interleukin. TNFα=tumour necrosis factor α.

Screening tools for the hospital setting

Malnutrition is diagnosed in a phased approach. The first phase consists of nutritional screening to identify patients who are at risk of malnutrition. Professional societies recommend screening for malnutrition within the first 24–48 h of hospital admission, and at regular intervals thereafter, to rapidly and accurately identify individuals who need to be referred to a specialist for nutritional assessment and possible intervention.[26] Various malnutrition screening tools exist to detect potential or manifested malnutrition during admission of a patient to hospital.[18, 27] Screening and assessment tools need to be easy to use in clinical practice, require minimal training of personnel, and be broadly applicable to all patients being admitted to hospital. However, a detailed nutritional assessment requires skilled nutrition specialists to establish if a patient has, or is at risk of, malnutrition and the extent and causes of it.

As the majority of screening components have little sensitivity and specificity when used independently, screening tools that identify patients who are at risk of developing malnutrition require inclusion of several parameters. High levels of validity, agreement, and reliability in malnutrition screening tools are desirable to ensure correct identification (without under-referrals or over-referrals) and the prompt treatment of patients who are malnourished. For the selection of the appropriate screening tool, it is important to understand whether the tool was validated for the patient population (eg, age and medical condition) and setting of interest (eg, hospital, institutional, or community setting). Table

1 provides details of effective screening and assessment tools for adults, including an overview of their validity, agreement, and reliability.[27-33]

Table 1. Characteristics of major nutrition screening and assessment tools for adults

	Parameters assessed	Possible outcomes	Recommended setting	Validity, agreement, and reliability to screen for malnutrition*
Nutritional Risk Screening[27]	Weight loss; reduced food intake in the past week; BMI; impaired general condition; severity of disease; and age	Nutritional risk (≥3 points) and no nutritional risk (<3 points)	Adults admitted to hospital	Moderate validity and agreement; reliability not reported
Malnutrition Universal Screening Tool[28]	Weight loss; BMI; and reduced food intake for ≥5 days (acute disease)	Low risk of malnutrition; medium risk of malnutrition; and high risk of malnutrition	Adults outside of hospital and adults admitted to hospital and other care settings	High validity; moderate agreement and reliability
Mini Nutritional Assessment-Short-Form[29]	Reduced food intake during the past 3 months; weight loss during the past 3 months; mobility; psychological stress or acute disease; neuropsychological problems; and BMI or calf circumference	Normal nutritional status; at risk of malnutrition; and malnourished	Older adults living in institutional settings and older adults not in hospital	Moderate validity and reliability; low agreement
Malnutrition Screening Tool[30]	Weight loss and reduced food intake	Low risk of malnutrition; medium risk of malnutrition; and high risk of malnutrition	Older adults living in institutional settings and adults admitted to hospital	Moderate validity, agreement, and reliability
Short Nutritional Assessment Questionnaire[31]	Weight loss; decreased appetite; and use of supplemental drinks or tube feeding	No intervention; moderately malnourished; and severely malnourished	Adults admitted to hospital	Moderate validity and reliability; agreement not reported
Subjective Global Assessment[32]	Weight loss; reduced food intake; gastrointestinal symptoms; functional capacity; comorbid illness and its relation to nutritional requirements; and brief physical examination	Well nourished; mildly or moderately malnourished; and severely malnourished	Adults admitted to hospital and adults not in hospital	Moderate validity, agreement, and reliability

BMI=body-mass index.

*Validity, agreement, and reliability according to Skipper and colleagues.[33]

Diagnostic criteria for disease-related malnutrition and nutritional assessment

The second step in the diagnostic pathway is to apply specific criteria to substantiate the diagnosis of malnutrition in patients admitted to hospital. The Global Leadership Initiative on Malnutrition (GLIM) has published the most recent of these specific criteria.[12, 13] GLIM proposes a straightforward two-step approach to diagnosis of disease-related malnutrition, with an initial screening to identify patients who are at risk that is followed by a more in-depth assessment to diagnose malnutrition and grade its severity (figure 2).[12, 13] Although several methods have been proposed in the past,[15] GLIM was designed to provide a more specific diagnosis of malnutrition and includes three phenotypic criteria (unintentional weight loss, low body-mass index [BMI], and reduced muscle mass) and two aetiological criteria (reduced food intake or assimilation and increased inflammation or disease burden). On the basis of the GLIM criteria, at least one phenotypic criterion and one aetiological criterion must be present to reach a diagnosis of malnutrition. Phenotypic metrics for grading severity (stage 1 [moderate] and stage 2 [severe] malnutrition) have been proposed. GLIM recommend that the aetiological criteria be used to guide intervention and anticipate outcomes. The GLIM criteria support classification of malnutrition into four aetiology-related diagnosis categories (figure 2).

During the diagnostic process, it would be ideal to distinguish malnourishment from other descriptive syndromes, such as sarcopenia, cachexia, and frailty. Although reduced muscle mass is a criterion for malnutrition in all current diagnostic criteria, it is also the hallmark feature of other descriptive syndromes. Cachexia refers to severe weight loss and wasting associated with cancer, HIV, and other severe illnesses. Although there are similarities between definitions of cachexia and malnutrition, inflammation and cytokines seem to be key components of cachexia, whereas malnutrition includes these components and starvation-related phenomena.[34, 35] Frailty refers to poor homoeostasis after an acute illness and is a consequence of the cumulative decline in many physiological systems.[36] Phenotypically, frailty is often associated with unintentional weight loss, self-reported exhaustion, muscle weakness, slow walking speed, and low physical activity,[8] but can also be viewed as the longer-term effect of malnutrition or cachexia. Some experts have suggested that malnutrition is the higher-order taxonomical term and that cachexia, sarcopenia, and frailty are different subtypes of the same condition.[8] However, it is controversial whether these different syndromes are variations of the same common condition and need a common approach to diagnosis and treatment, or whether they are truly different disorders that merit distinct treatment strategies.

Although the criteria proposed by GLIM are new, the content, criteria, and predictive validities of this tool have been assessed in many cohorts worldwide and, hopefully, they will become part of routine clinical practice for diagnosing malnutrition in a consistent manner.[12, 13] However, there is still a need for prospective validation of these criteria in different patient populations and disease states, and the response to nutritional therapy in patients diagnosed as malnourished with the GLIM criteria is not known. Hence, GLIM is considered an evolving concept. The proponents of GLIM recognise this and plan re-evaluation every 3–5 years as new studies become available.[14, 37]

Step 1: screening for nutritional risk

Use of validated screening tool (NRS)

	Impaired nutritional status	Points	Severity of the disease	Points
Absent	Normal nutritional status	0	Normal nutritional requirements	0
Mild	Weight loss >5% of bodyweight in 3 months or food intake <50–75% of normal in the preceding week	1	Patients admitted to hospital due to complications associated with chronic diseases	1
Moderate	Weight loss >5% in 2 months; BMI 18·5–20·5 kg/m² and impaired general condition; or food intake 25–50% of normal in the preceding week	2	Patients confined to bed due to illness	2
Severe	Weight loss >5% in 1 month; BMI <18·0 kg/m² and impaired general condition; or food intake 0–25% of normal preceding week	3	Patients on intensive care units	3

+1 point if the patient is aged ≥70 years

If NRS score is ≥3 then patient is nutritionally at risk

Step 2: diagnosis of malnutrition

GLIM criteria

Phenotypic criteria		
Weight loss	**Low BMI**	**Reduced muscle mass**
>5% of bodyweight in the past 6 months or >10% of body weight in >6 months	<20 kg/m² (<18·5 kg/m² for Asian patients) for patients <70 years or <22 kg/m² (<20 kg/m² for Asian patients) for patients ≥70 years	Validated with body composition measuring techniques (eg, DXA, BIA, CT, and MRI)

Aetiological criteria	
Reduced food intake or assimilation	**Inflammation**
≤50% of energy requirement met by food intake for >1 week; any reduction in food intake for >2 weeks; or any chronic gastroenterological condition that adversely affects food assimilation or absorption	Acute disease (or injury) or chronic disease-related inflammation

Diagnosis of malnutrition if the patient has ≥1 from the phenotypic criteria and ≥1 from the aetiological criteria

Figure 2. Current approach to screening and diagnosis
Approach to screening is according to NRS-2002[27] and diagnosis is according to GLIM.[12, 13] BIA=bioelectrical impedance analysis. BMI=body-mass index. DXA=dual-energy x-ray absorptiometry. GLIM=Global Leadership Initiative on Malnutrition. NRS=Nutritional Risk Screening.

This proposed approach, screening for the risk of malnutrition that is followed by establishment of the diagnosis, should be complemented with a more detailed nutritional

assessment to provide the foundation for individualised nutrition care plans. A nutritional assessment can comprehensively and objectively evaluate nutritional status. Nutritional assessment can include a dietary history (eg, food recall, food frequency questionnaires, and digital imaging technology to monitor food intake),[38] physical examinations (eg, signs of severe subcutaneous loss, muscle wasting, and oedema), anthropometric measurements (eg, weight, height, BMI, mid-arm or calf circumference, and skinfold thickness), functional tests (eg, handgrip strength),[39] functional status or independence (eg, Barthel index),[40] body composition (eg, bioelectrical impedance analysis, dual-energy x-ray absorptiometry, CT, MRI, and isotope dilution methods), quality-of-life questionnaires, and laboratory values (eg, haemoglobin, C-reactive protein, albumin and prealbumin protein [transthyretin], creatinine, ferritin, zinc, vitamin [folate, vitamin B12, and vitamin D], and urea and electrolyte concentrations). The presence of a skilled nutritional specialist to interpret information obtained from the assessment is imperative. Accurate interpretation will result in more individualised and, thus, more effective nutritional intervention and monitoring.

Nutritional interventions to improve clinical outcomes in the hospital setting

The association of malnutrition with increased risks for adverse clinical outcomes and mortality has been well documented in several observational studies.[3, 5, 15] However, the findings of several randomised controlled trials have sparked a new debate on best nutritional care practices in the hospital setting. Evidence of the benefits of nutritional interventions for medical inpatients is compelling. A systematic review and meta-analysis on nutritional therapy in inpatients with medical conditions found significantly improved clinical outcomes in those receiving adequate nutritional therapy compared with those receiving no nutritional therapy.[41] The review included 27 randomised controlled trials from several countries comprising 6803 inpatients and reported a 27% reduction in mortality and non-elective hospital readmissions.[41] Yet, there was some heterogeneity among trials and several studies (particularly the oldest ones) were at high risk for bias. In addition, wide variations in the treatment of control group patients were observed, reflecting differences in standards for what is considered usual practice for nutritional care.

Table 2 provides a summary of the six most recent trials (published since 2015) on nutritional therapy for patients who are malnourished or at risk of malnutrition and were admitted to hospital.[42-47] The largest trial included in table 2 was EFFORT, which was a pragmatic, randomised controlled multicentre trial in Switzerland and included more than 2000 patients at risk of malnutrition (Nutritional Risk Screening total score of ≥3).[43] EFFORT analysed the effects of individualised nutritional therapy, which aimed to reach energy, protein, and micronutrient requirements, compared with standard hospital food. The primary composite endpoint of the trial was severe complications, mortality, admission to the intensive care unit, cardiovascular and gastrointestinal complications, functional decline, and hospital readmission. In this trial, nutritional intervention was effective in lowering the risk of mortality with a number needed to treat of 37 patients.[43] A similar positive effect on the risk of mortality (number needed to treat of 20 patients) was also found in the second-largest, placebo-controlled trial, NOURISH.[47] NOURISH compared the use of specialised protein-rich oral supplements with placebo on clinical outcomes in 652 patients from multiple centres across the USA. Although the trial was negative regarding its primary composite endpoint (90 day post-discharge incidence of death or non-elective readmission

to hospital), there was a significant reduction in 90 day mortality in the group given protein-rich oral supplements. Studies in specific medical populations also exist. In a trial, which studied nutritional intervention for patients admitted to hospital for acute heart failure, the nutritional intervention group had reduced rates of mortality and repeat admission to hospital compared with the standard-of-care group.[46] Another study that included patients with pneumonia in hospital found that nutritional intervention lowered the risk for disease-specific readmission rates,[42] but did not significantly improve mortality. Similarly, in two smaller trials,[44, 45] patients given individualised nutrition plans did not have a significant reduction in mortality but did have a shorter length of hospital stay than patients given standard care.

Although these trials had different approaches to nutritional intervention, they did share concepts. First, most trials initially screened admitted patients for the risk of malnutrition, which was followed by a thorough assessment of nutritional status by multidisciplinary teams (including dietitians, nurses, and physicians) to identify patients with disease-related malnutrition who might benefit from nutritional therapy. A detailed clinical assessment is important to identify side-effects of medications and medical illnesses, such as gastrointestinal and metabolic conditions, which can cause loss of appetite, difficulties in feeding, or malabsorption. Once a diagnosis of disease-related malnutrition has been established, guidelines recommend defining individual nutritional goals, including energy and protein intake, micronutrient intake, and other disease-specific targets.[2, 48] Energy expenditure, on which most nutritional interventions are based, can be estimated with indirect calorimetry or a validated formula (eg, adapted Harris–Benedict equation).[49] Validated formulae consider the resting metabolic rate and effects of any disease. In everyday clinical practice, simple weight-based formulas (eg, 25–30 kcal/kg of bodyweight per day) have also been valuable in estimating energy requirements.[2] A high protein intake of 1·2–1·5 g/kg per day has been shown to improve clinical outcomes in adult patients (≥18 years) who are treated in hospital for medical conditions,[43, 47] except in those with kidney failure, in which lower targets of 0·8 g/kg per day were used in one trial.[43] However, the definition of optimal protein targets for patients with chronic kidney disease still needs additional research.[48] Some procedures (eg, dialysis and paracentesis) can remove proteins from the body and these losses should also be included in the total daily protein requirements. According to consensus guidelines, multivitamin and multimineral supplements are also important adjuncts to correct micronutrient deficiencies.[2, 48] Once energy requirements are estimated, a nutritional plan to reach these requirements should be established (preferably with the help of a dietitian) with an initial adoption of an oral diet plan (eg, meals selected according to patient preferences, food fortification, snacks, and oral nutritional supplements).[48] If energy and protein targets cannot be reached orally, nutritional therapy should be escalated to enteral or parenteral feeding. Regular monitoring is essential to adjust the nutritional protocol. Figure 3 shows a pragmatic treatment algorithm for malnutrition in the inpatient setting that is based on a consensus conference[48] and a subsequent validation trial.[43]

Table 2. Overview of six nutritional trials with medical inpatients

	Country	Number of participants	Type of study	Population	Screening tool	Nutritional intervention during hospital admission	Intervention after discharge	Effect on mortality (OR [95% CI])	Other results
Yang et al[42]	Taiwan	82	Single centre RCT	Aged ≥65 years and primary diagnosis of pneumonia	BMI <18·5 kg/m^2 or MNA-SF score ≤7	Individualised nutritional intervention programme	Telephone calls	0·69 (0·26–1·86)	Daily calorie and energy intake increased; readmission rate for pneumonia decreased
Schuetz et al[43]	Switzerland	2088	Multicentre RCT	General medical inpatients who had an expected length of hospital stay of ≥4 days and were aged ≥18 years	NRS ≥3	Systematic nutritional assessment to define nutritional targets, followed by a step-up treatment algorithm (oral, enteral, or parenteral)	..	0·71 (0·52–0·97)	Adverse outcomes decreased; decline in functional status decreased; quality of life increased
Cano-Torres et al[44]	Mexico	55	Single centre RCT	Aged ≥20 years and admitted to medical wards	NRS ≥3	Individualised nutrition plan according to energy and protein intake requirements; dietary advice for patients, caregivers, or family members	..	0·16 (0·02–1·50)	Length of hospital stay decreased

	Country	Number of participants	Type of study	Population	Screening tool	Nutritional intervention during hospital admission	Intervention after discharge	Effect on mortality (OR [95% CI])	Other results
Sharma et al[45]	Australia	148	Single centre RCT	Aged ≥60 years and admitted to acute medical ward	PG-SGA class B or C	Individualised nutrition care plan	Monthly post-discharge telehealth follow-up for 3 months	0·73 (0·31–1·70)	Length of hospital stay decreased
Bonilla-Palomas et al[46]	Spain	120	Multicentre RCT	Aged ≥18 years and admitted to hospital for acute heart failure	MNA score <17 points	Individualised intervention that included diet optimisation, specific recommendations, and nutritional supplement prescriptions	Ongoing therapy for 6 months	0·28 (0·13–0·63)	Readmission rate due to heart failure decreased
Deutz et al[47]	USA	652	Multicentre placebo-controlled RCT	Aged ≥65 years and admitted to medical wards with a primary diagnosis of congestive heart failure, acute myocardial infarction, pneumonia, or chronic	SGA class B or C	Two servings of oral nutritional therapy (high-protein β-hydroxy β-methylbutyrate) per day	Continuation of nutritional treatment for 90 days	0·47 (0·25–0·89)	Nutritional status and bodyweight increased

	Country	Number of participants	Type of study	Population	Screening tool	Nutritional intervention during hospital admission	Intervention after discharge	Effect on mortality (OR [95% CI])	Other results
				obstructive pulmonary disease					

BMI=body-mass index. MNA=Mini Nutritional Assessment. MNA-SF=Mini Nutritional Assessment-Short Form. NRS=Nutritional Risk Screening. OR=odds ratio. PG-SGA=Patient-Generated Subjective Global Assessment. RCT=randomised controlled trial. SGA=Subjective Global Assessment.

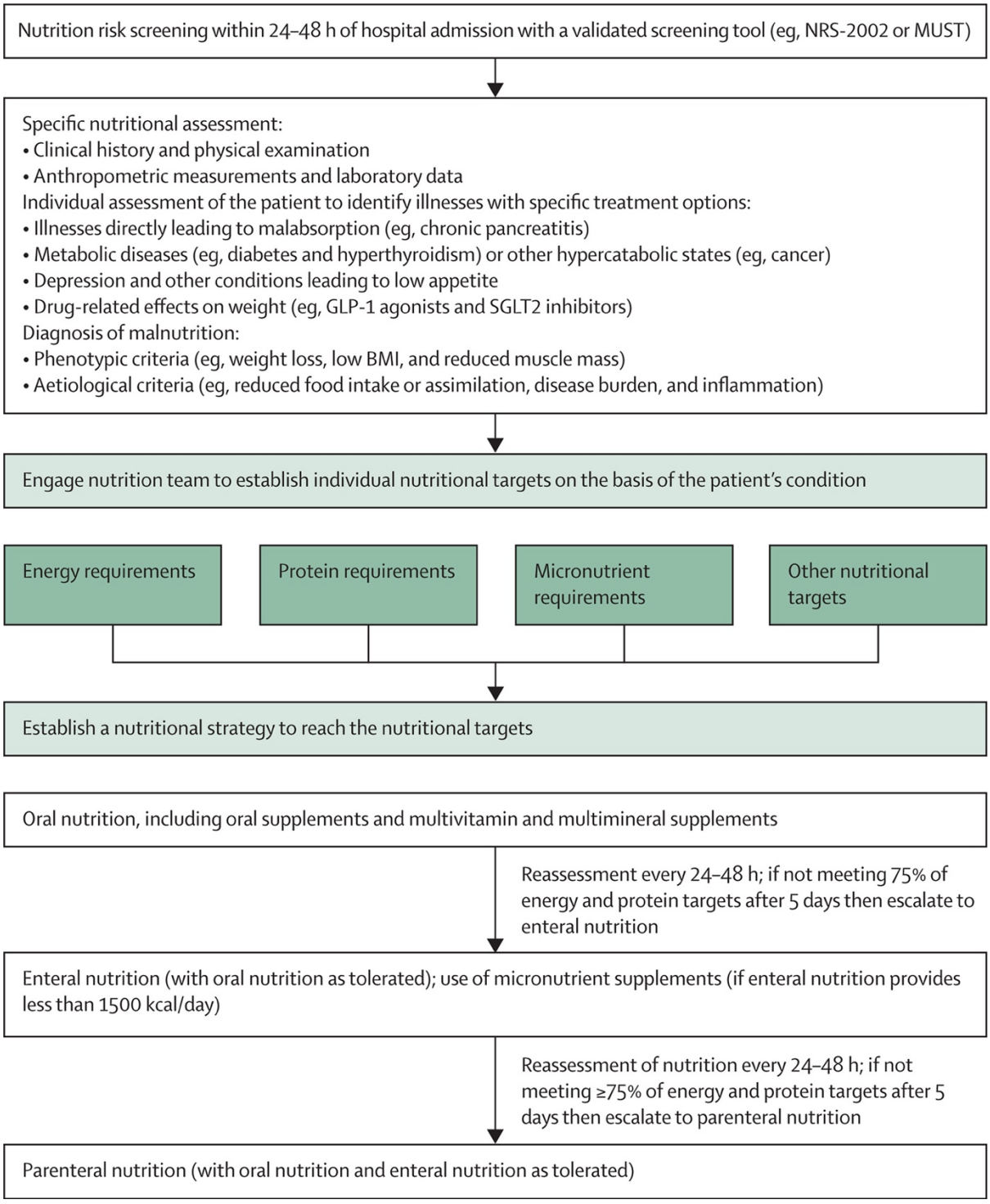

Figure 3. Treatment algorithm for hospitalised patients at risk of malnutrition
BMI=body-mass index. GLP-1=glucagon-like peptide-1 (pro-glucagon). MUST=Malnutrition Universal Screening Tool. NRS=Nutritional Risk Screening. SGLT2=sodium-glucose cotransporter-2.

The considerations in figure 3, regarding initiating nutritional therapy during the hospital stay of medical inpatients, identified by screening and assessment, are in line with evidence-based clinical practice guidelines regarding the nutritional approach for patients with multimorbid conditions,[2] and older adult patients,[50] from the European Society for Clinical

Nutrition and Metabolism (ESPEN) and the American Society for Parenteral and Enteral Nutrition (ASPEN).[51]

Although there is wide consensus about the beneficial effects of energy and protein to reach nutritional goals in patients who are malnourished, the role of specific formulas enriched with fibre, immunonutrients (eg, omega-3 fatty acids, arginine, glutamine, RNA, and nucleotides), or other nutrients has not been well studied in medical inpatients.[2] The NOURISH trial found clinical benefits of high-protein oral nutrition supplementation containing β-hydroxy β-methylbutyrate compared with placebo.[47] However, it is unclear whether the maintenance of muscle mass during hospital stay and significant decrease in post-discharge mortality observed in this study were due to the specific product, the high levels of protein, the micronutrients provided by the supplement used in the intervention group, or any combination of these.

Refeeding syndrome

Although nutritional therapy is generally considered safe with low risk for complications, particular attention to refeeding syndrome is important. Refeeding syndrome is a life-threatening metabolic complication that is caused by rapid feeding in combination with inadequate provision of micronutrients and electrolytes (eg, phosphate, potassium, magnesium, and vitamin B1). Refeeding syndrome can occur with oral, enteral, or parenteral nutrition[52] and it is often not recognised and, therefore, not treated appropriately.[53] Oral and enteral nutrition has a higher risk of refeeding syndrome than parenteral nutrition due to the incretin effect.[54] In one nutritional trial in patients fed orally, parenterally, or via the nasogastric route, 15% of patients had refeeding syndrome, which was associated with increased 180 day mortality rates, 180 day intensive care unit admission rates, and length of hospital stay.[55] In one consensus paper, diagnostic criteria for imminent refeeding syndrome have been defined as a decrease in electrolyte concentrations—eg, a >30% decrease from baseline or an absolute value of ≤0·6 mmol/L of phosphate concentration, or any other electrolyte (eg, magnesium or potassium) below the normal range—within 72 h of starting nutritional therapy.[56] In addition, manifest refeeding syndrome is considered if any electrolyte shifts occur in combination with typical clinical symptoms (eg, oedema, tachycardia, and tachypnoea).[56] An ASPEN interprofessional taskforce defined refeeding syndrome with a formulation similar to the one listed in the consensus paper,[56] the main difference being that no distinction was made between imminent and manifest clinical situations.[57] Risk assessment, establishment of a care plan, and monitoring of patients throughout nutritional therapy are important to reduce refeeding syndrome-related morbidity. The UK National Institute for Health and Care Excellence criteria (low BMI; substantial unintentional weight loss; insufficient nutritional intake; low concentrations of potassium, phosphate, or magnesium before feeding; or a history of alcohol or drug use, including insulin, chemotherapy, antacids, or diuretics) are helpful for identification of patients at high risk of refeeding syndrome, with starvation being the predominant risk factor.[58] Unless plasma concentrations of electrolytes are high, patients at risk of refeeding syndrome should receive generous prophylactic provision of electrolytes (eg, 2–4 mmol/kg per day of potassium, 0·3–0·6 mmol/kg per day of phosphate, and 0·2–0·4 mmol/kg per day of magnesium).[58] In a patient who has been starved, plasma electrolyte concentrations do not reflect whole body status and there could be a substantial

intracellular depletion, particularly as 98% of potassium is intracellular.[52, 58, 59] Additionally, patients should receive vitamin B1, 200–300 mg/day) and multivitamin supplements immediately before and during the first 10 days of feeding.[58] In patients at risk of refeeding syndrome, excess sodium and fluid can also be dangerous, and an intake of less than 1 mmol/kg per day of sodium and 20 mL/kg per day of fluid is recommended in the early phase of refeeding.[52, 59] Nutritional therapy should be started with reduced energy goals and increased slowly to the full caloric requirements during 5–10 days, according to the individual risk classification of refeeding syndrome.[56] Electrolyte concentrations should be monitored daily during the period that the patient is suspectable to refeeding syndrome, alongside additional clinical examination with special attention to hydration status and parameters to detect signs and symptoms of fluid overload or micronutrients deficiency.

Personalised nutrition and malnutrition biomarkers during treatment in hospital

Understanding the pathophysiology of malnutrition is key to developing effective new interventions. Translational research in the pathophysiology of malnutrition is expanding rapidly. Although there is currently a strong consensus that nutritional protocols should be individualised regarding nutritional targets for inpatients (based on their BMI and severity of illness) in critical care and hospital ward settings, current research suggests that tailoring nutrition to the specific medical illness of patients could also improve the effectiveness of nutritional intervention. This concept of personalised nutrition is based on the observation that not all patients show the same response to nutritional interventions. Whether or not a patient benefits from nutritional therapy might relate to illness-specific factors (eg, comorbidities, inflammation, and acute *vs* chronic course) or patient-specific factors (eg, age and genetic vulnerability). Biomarkers and key predictors of these factors might improve the individualised approach when treating a patient with malnutrition. Several effect-modifying conditions and parameters have been proposed and tested empirically (table 3).[39, 42, 46, 60-69] Currently, the acuteness of the disease and systemic inflammation (the key driver of disease-related reduction in appetite), reduced food intake, and muscle catabolism seem to predict the response to nutritional treatment.[69-71] In a secondary analysis of EFFORT, stratification for C-reactive protein concentration at admission showed that patients with high levels of inflammation (C-reactive protein >100 mg/L) did not have decreased mortality when receiving individualised nutrition therapy compared with patients who did not receive individualised nutrition, a finding that was significant in interaction analyses.[69] This result could explain the differences in clinical results depending on the clinical setting—namely, the absence of a response to individualised nutrition in studies done in patients who have critical illness or advanced cancer. It is not known whether low-grade inflammation, typically seen in patients with obesity or diabetes, also needs attention. Another modifying condition is chronic kidney disease, as patients with reduced kidney function showed a stronger response to nutritional treatment than those with healthy kidney function.[43]

Despite these findings, specific blood biomarkers of malnutrition are not yet available in routine clinical care. Research in this area is complex due to differing views of the definition of malnutrition, the absence of a strong reference definition, the existence of several pathophysiological pathways, and the influence of underlying clinical illnesses and multimorbidity on nutrition markers.[72] For example, despite being used as markers in

the past, albumin and prealbumin concentrations are now recognised to be strongly influenced by disease-related factors such as inflammation, liver function, fluid balance, and metabolism. Despite being highly predictive of morbidity and mortality, they do not reflect the adequacy of nourishment.[73] A position paper from ASPEN highlights that, although there is an association between inflammation and malnutrition, there is no association between malnourishment and visceral-protein concentrations.[74] As such, serum albumin and prealbumin should not be used as surrogate measures of total body protein, total muscle mass, or status of nourishment, but can provide prognostic information, such as disease-related muscle wasting in the absence of starvation.[73]

Table 3. Potential effect-modifying factors regarding personalised nutritional therapy in patients treated in hospital on medical wards

	Rationale	Evidence	Exemplary findings of personalised nutritional therapy
Medical conditions			
Heart failure	High prevalence of malnutrition; elevated cytokine concentrations and inflammation causing loss of appetite; and intestinal oedema leading to malabsorption (cardiac cachexia)	RCTs with a small sample size and a meta-analysis with heterogeneous trials	Bonilla-Palomas and colleagues[46] showed reduced all-cause mortality rate and reduced readmission rates; a meta-analysis[60] showed that patients given personalised nutritional therapy had increased bodyweight; and a secondary analysis of an RCT[61] showed reduced mortality and major cardiovascular events
Cancer	High prevalence of malnutrition; cytokine-driven systemic inflammation leading to reduction in appetite and food intake; muscle loss (tumour cachexia); and side-effects of tumour therapy	Meta-analyses of several trials from the outpatient setting; tumour-specific or therapy-specific trials; and a retrospective propensity score-matched analysis	A meta-analysis[62] showed the positive effect of personalised nutritional therapy on nutritional intake and quality of life, but not on mortality; a meta-analysis[63]showed an increase of bodyweight in patients receiving chemoradiotherapy; an RCT[64] showed the positive effect on long-term outcomes in patients with colorectal carcinoma who are having radiotherapy. A large propensity score-matched retrospective analysis,[65] with different cancer types, showed lower risk of in-hospital mortality and discharge to a post-acute care facility for inpatient care in a heterogeneous cancer population than without nutritional therapy; and a secondary analysis of an RCT[66] showed lower mortality in patients with different types of cancer than in patients without nutritional therapy

	Rationale	Evidence	Exemplary findings of personalised nutritional therapy
Chronic kidney disease and dialysis	High risk for malnutrition; accumulation of nitrogen-containing products from dietary and intrinsic protein catabolism negatively affects appetite and taste; uraemia reducing gastrointestinal nutrient absorption; and side-effects of medication	Insufficient evidence for the treatment of malnutrition from a secondary analysis; protein intake goals are controversial because of recommendations of protein restriction	A secondary analysis of an RCT[67] with medical inpatients at nutritional risk showed kidney function at admission was a strong predictor for the response to nutritional therapy
Lower respiratory tract infection	Malnutrition is frequent in patients with lower respiratory tract infection	Some evidence from an RCT with a small sample size and secondary analysis; high-quality evidence is sparse for patients with COVID-19 who are not critically ill	An RCT[42] showed nutritional therapy reduced readmission rates for pneumonia; and a secondary analysis of an RCT[68] showed a positive effect on 30 day mortality
Strength and muscle function			
Handgrip strength	Handgrip strength is an easy-to-use tool to assess muscle strength in clinical practice and is endorsed by numerous international clinical nutrition guidelines due to the known association of low handgrip strength with poor clinical outcomes	Insufficient evidence	A secondary analysis of an RT[39] showed that patients with low handgrip strength can benefit from nutritional therapy
Laboratory parameters			
Albumin and prealbumin (transthyretin)	Often considered as nutritional markers	No evidence regarding predictive value for response to nutritional therapy	..
C-reactive protein	Inflammation often has a role in the pathophysiological mechanisms of malnutrition; inflammation leads to insulin resistance and reduction of appetite	Evidence from secondary analysis that is similar to results from trials in intensive care units	A secondary analysis of an RCT[69] showed no effect of nutritional therapy in patients with high C-reactive protein concentrations

RCT=randomised controlled trial.

Knowledge about the role of the gut microbiota on several aspects of health has also been increasing in the past years. A new microbiota-directed supplement has been shown to effectively treat malnutrition in children in low-income settings, leading to improved growth and weight gain.[75] Additional research will be needed to establish whether these promising

results from children who are malnourished in low-income settings can be extrapolated to adults who are malnourished as inpatients.

Long-term nutritional therapy after hospital discharge

In the long term, patients with malnutrition have a high risk of disease-related mortality. Meta-analyses of trials in patients who have been discharged from hospital showed beneficial effects of ongoing nutritional therapy with regards to energy and protein intake and bodyweight, but no effect on mortality.[76-78] A long-term follow-up study of patients in the EFFORT trial reported a substantial increase in 5 year mortality risk related to nutrition risk score, increasing from approximately 50% to approximately 60%, with Nutritional Risk Screening-2002 score increasing from 3 to 5.[79] Nevertheless, the effects of nutritional therapy that was stopped at hospital discharge did not show a legacy effect after 6 months.[79] Yet, several trials (such as the NOURISH trial) that offered continued nutritional therapy in the outpatient setting after discharge from hospital have reported significant beneficial effects of nutritional therapy on mortality over time.[46, 47, 80] Thus, there is evidence to support the continuation of individualised nutritional therapy after discharge from hospital for patients with existing risk of (or manifested) malnutrition. However, additional research is needed to support this hypothesis in an adequately powered trial.

Ethical considerations

Although nutritional interventions are recommended for most patients who need them, guidelines advise that special considerations should be given to patients without capacity and those on palliative care.[81, 82] The important ethical principles in the doctor–patient relationship, including autonomy (principle of self-determination and recognition of the patient's rights), beneficence (the view that the patient should be provided with some form of benefit), non-maleficence (the deliberate avoidance of harm), and justice (the fair and equitable provision of available medical resources to all) should guide the decision-making process and there should be clear communication between the treating team, patient, and caregivers. Advance directives and proxies should be taken into consideration and discussions should be had about the potential futility of treatment and the net benefit to the patient before starting or stopping artificial nutritional therapy. Legal advice or court orders might have to be sought when there is disagreement between the treating team and the patient or their caregivers.[81, 82]

The provision of food or water by mouth is generally considered part of basic care, which includes procedures deemed essential for patient comfort. Health-care professionals are duty-bound to ensure the provision of basic care to all patients, unless actively resisted by the patient.[82] Therefore, voluntary cessation of eating and drinking is ethically acceptable if done on the basis of a competent patient's wishes or advance directives.

Outlook and future considerations

The optimal use of individualised nutritional therapy to effectively prevent and treat malnutrition is complex and constitutes a major area of current research. Specifically, the ideal time to initiate nutritional therapy in the hospital setting and the optimal duration

have not been well established. There is consensus that prevention of malnutrition is better than treatment, as data show that patients with advanced cachexia can have minimal response to nutritional treatment. Additionally, as patients with malnutrition have a substantial long-term risk of mortality and morbidity, there is great interest in researching long-term nutritional therapy that happens after discharge from hospital. A better understanding of the phenotypes of malnutrition is also needed to develop more personalised approaches in the future. A first step to the optimal use of nutritional therapy would be to better distinguish between malnutrition (ie, a multi-cause syndrome) and being malnourished (ie, a patient that received inadequate feeding). Because the underlying condition can predict the response to nutritional treatment, a patient with malnutrition due to inadequate feeding might need a different nutritional approach regarding the quantity and quality of feeding to a patient who is wasted from disease or in a state of severe inflammation. Although high protein and energy diets improve outcomes in patients who are medically stable, the same diet can cause hyperglycaemia and overfeeding in a patient who is metabolically stressed and critically ill, where modest provision of nutrients might be beneficial.[83, 84] Importantly, to advance the field, large-scale interventional trials are needed with thorough phenotyping of participants to study the predictors of response to nutritional therapy, which can later be used to arrive at personalised treatment decisions. For example, the EFFORT trial[43] has provided evidence that patients with chronic kidney disease have a more pronounced benefit from nutritional therapy than patients without chronic kidney disease[67] and that the same treatment in patients with high levels of inflammation did not influence clinical outcomes in medical inpatients.[69] Similarly, handgrip strength has been shown to be a predictor of response to nutritional therapy.[39] Understanding these factors will help change the general guideline recommendation approach to more individualised nutritional therapy for patients with malnutrition. In addition to advancing the science of medical nutrition, there needs to be a focus on improving the education of students and health professionals on all aspects of nutritional care.[85] Patients and their caregivers should be involved in the shared decision-making process before the start of nutritional therapy and this discussion should revolve around the BRAN concept (defined as understanding the benefits and risks of the interventions, considering alternative therapy, and knowing the consequences of doing nothing).[86] Fully informed patients who have been involved in shared decision making are best equipped to assume responsibility and be partners in their own medical care.

Contributors

PS and FG did the literature search; PS and NK-B created the figures; all authors participated in writing and reviewing of the manuscript. All authors read and approved the final manuscript.

Declaration of interests

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