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Assessing the Clinical Applicability of Malnutrition Biomarkers: Proceedings from a Scientific Roundtable

SUMMARY

Renowned experts convened in Chicago, Illinois on June 8, 2016 to assess the clinical applicability of malnutrition biomarkers based on emerging research. Abbott Nutrition Research & Development and the Abbott Nutrition Health Institute (ANHI) hosted the scientific roundtable. Discussion targeted strengths and limitations of nutrition screening and assessment tools in different clinical practice settings and patient populations, novel assessment tools, and current research in identifying or developing valid malnutrition biomarkers for enhanced nutrition intervention.

Abbott Nutrition Roundtable Faculty and Speakers

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INTRODUCTION (Jacqueline Boff, PhD)

There is growing concern among some clinicians that malnutrition is both underappreciated and underdiagnosed, and objective screening tools are needed. Malnutrition screening, assessment and diagnosis may require different parameters for varying patient populations, eg, general hospitalized patients, intensive care unit (ICU) patients, renal patients, the elderly, and patients with frailty and sarcopenia. Practices in the U.S. were compared with ESPEN guidelines (European Society for Clinical Nutrition and Metabolism). This roundtable focused on the need, viability for development and use, and compliance of biomarkers for malnutrition.

NUTRITION SCREENING AND ASSESSMENT – CURRENT PRACTICES AND FUTURE NEEDS
(Stephen A. McClave, MD, FASPEN)

Nutrition assessment, as well as the concept of malnutrition itself, is not well defined, standardized, or validated in the literature. The nutrition assessment of the hospitalized patient is an ongoing process that starts with the initiation of feeding, and is not completed until the patient is discharged from the hospital and/or advanced to an oral diet. Any search for biomarkers to be used with nutrition assessment needs to be relevant to clinical practice. They should be markers that change practice, taking into account their cost, availability, and reimbursement. The marker has to add value to other assessment tools in the intensive care unit (ICU). The ongoing process of nutrition assessment starts with a determination of nutritional risk, but goes on to identify energy and protein goals, evaluate tolerance, and monitor adequacy of nutrition therapy delivery.[1]

Information obtained from nutrition assessment does have prognostic value. Evidence of gastrointestinal intolerance identifies a patient at greater risk for adverse outcomes. Comparison between patients with tolerance of enteral feeding versus those with intolerance, shows prolonged duration of ICU and hospital length of stay, with increased mortality in those with intolerance.[2] Nutritional biomarkers involving serum protein levels are misleading and invariably reflect the acute phase response. Decreases in protein levels in response to injury invariably reflect increased vascular permeability, hepatic reprioritization of protein synthesis, and the catabolism of albumin by the body as a source for the antioxidant cysteine.[3] One of the most important aspects of nutrition assessment focuses not on defining malnutrition but identifying **nutritional risk**, a process which is driven by both disease severity and

nutritional status. Identifying high nutritional risk indicates that patient who requires closer to goal feeding, for whom adequate nutrition therapy will actually change clinical outcome. Important issues in nutrition assessment now are risk assessment and combining nutrition assessment with an evaluation of disease severity in critical illness.[4]

Assessing energy and protein requirements are integral to nutrition assessment. While little has changed in our assessment of caloric requirements, we are now putting greater emphasis on protein requirements, pushing to higher doses, and minimizing restrictions on the delivery of protein. New aspects of nutrition assessment focus on computed tomography (CT) scanning and ultrasound to follow changes in lean body mass. Developing ways to measure not only muscle mass, but functionality, is an important aspect to predict recovery and outcome following discharge from the ICU.[5]

Indirect calorimetry should be used to a greater extent, as published predictive equations are inaccurate [especially with the wide range of body mass index (BMI) found in the ICU]. Indirect calorimetry provides a much better marker for requirements and, therefore, goal of nutrition therapy. Focusing on those parameters of nutrition assessment that do affect outcome and minimizing time on less relevant markers is an important paradigm shift for the clinician. Close scrutiny of serum protein levels should be replaced by an assessment of muscle function, muscle mass, and micronutrient deficiencies. Markers of inflammation and infection are emerging, but cost and availability may limit their impact. Ongoing clinical parameters need to be re-evaluated, with particular attention to reducing the emphasis on use of gastric residual volumes. Delivery of enteral nutrition should be monitored for adequacy, evaluating interruptions, minimizing inappropriate cessation, and reducing the duration of periods where patients are made NPO. Having protocols in place and enforcing those protocols are an important part of the delivery process. Identifying risk of aspiration and taking steps to reduce that risk are valuable, such as diverting the level of infusion lower in the GI tract, switching from bolus to continuous infusion, initiating prokinetics, and having nurses swab the oropharynx with chlorhexidine. Assessment of the access device is important, whether the route of nutrition therapy is parenteral or enteral. Periodic assessment of tube position by x-ray, and inspection of the access site of a percutaneous endoscopic device or central venous catheter are important (Figure 1).[6,7]

In summary, nutrition assessment is a full spectrum process which begins with initiation of feeding and continues through to advancement to oral diet and discharge from the ICU. Issues should focus on clinically relative parameters such as determination of nutritional risk, which patients need full feeds, and the design of a nutrition regimen appropriate for the clinical situation. Assessment should include a daily physical exam, monitoring signs of tolerance, following up on reasons for cessation or interruption in the feeds, and carefully following percent of protein/energy goals infused. Nutrition assessment has to be responsible for all issues related to delivery of nutrition therapy.

Nutrition Assessment Begins with Initiation of Feeding

C	Critical illness severity
A	Age
N	Nutrition risk screen
W	Wait for resuscitation
E	Energy protein requirements
F	Formula selection
E	Enteral access
E	Efficacy
D	Determine tolerance

Figure 1. CAN WE FEED?[7]

Novel Nutrition Screening and Assessment Tools in Intensive Care Unit Patients
(Sadeq A. Quraishi, MD, MHA, MMSc)
Critically ill patients are typically at risk for poor nutritional status at the time of intensive care unit (ICU) admission. They also tend to develop malnutrition over the course of their acute illness. And although it is widely accepted that nutritional status may influence clinical outcomes in the critically ill, rigorous studies, which support such conventional wisdom, are lacking. To date, one of the major reasons why such studies have been difficult to conduct is the lack of validated and standardized methods to assess nutritional status in ICU patients.

The Subjective Global Assessment (SGA) as well as the Nutritional Risk Screening (NRS) 2002 have been used widely to assess malnutrition risk in hospitalized patients. However, neither the SGA, nor the NRS 2002, have been validated in critically ill patients. Conversely, the Nutrition Risk in Critically Ill (NUTRIC) was recently validated in ICU patients and was shown to be associated with mortality.[8] Moreover, NUTRIC was shown to be superior to the SGA for identifying critically ill patients at increased risk for undesirable clinical outcomes.[9]

Here, we present data from our registry of nutritional parameters and clinical outcomes in ICU patients, which suggests that the NRS 2002 is not associated with either caloric or protein deficit over the course of critical illness. However, our data suggests that each unit increase in the NUTRIC score is associated with a 752 kcal (95%CI 448-1056 kcal) increase in caloric deficit, and a 49 g (95%CI 29-68 g) increase in protein deficit. We also found that in this cohort, the NRS 2002 was not associated with important clinical outcomes, but NUTRIC was associated with 30-day ventilator-free days (IRR 0.95: 95%CI 0.94-0.97), hospital length of stay (IRR 1.03: 95% CI 1.02-1.05), and 90-day mortality (OR 1.34: 95% CI 1.15-1.65).

Nonetheless, routine use of the NUTRIC may be limited by its inability to assess nutritional risk at ICU admission. Recently, a simple, novel tool, the Patient- And Nutrition-Derived Outcome Risk Assessment (PANDORA) score was developed and validated in a large international cohort of hospitalized patients, and PANDORA was shown to be a strong predictor of 30-day mortality.[10] Since it was not specifically tested in critically ill patients, we present data from our ICU registry that suggests PANDORA is comparable to the gold standard Acute Physiology And Chronic Health Evaluation (APACHE) II for predicting 30-, 90-, and 180-day mortality (AUC 0.69 vs. 0.73; p=0.29, AUC 0.71 vs. 0.74; p=0.52, and AUC 0.73 vs. 0.75; p=0.66, respectively). PANDORA has the advantage of being simple to calculate and can be performed upon ICU admission.

And finally, we address the growing scientific interest in the field of illness-related sarcopenia.[11] We present preliminary data on the use of non-invasive methods for assessing lean body mass (computed tomography [CT] and ultrasound), and discuss their associations with important clinical outcomes. Such organic measurements may provide a more functional assessment of nutritional status,[5] and may provide a more useful method of assessing the impact of nutrition interventions.

CI=confidence interval, IRR=incidence rate ratio, OR=odds ratio, AUC=area under the curve

The Malnutrition-Inflammation Score (MIS) and Its Clinical Application (Kamyar Kalantar-Zadeh, MD, PhD, MPH)
Patients with moderate to advanced chronic kidney disease (CKD) have exceptionally high mortality, mostly from cardiovascular events, high hospitalization, and poor quality of life. In these patients, most traditional cardiovascular disease risk factors do not explain the poor outcome.[12,13] Protein-energy wasting (PEW) and inflammation, together also known as the malnutrition–inflammation–cachexia syndrome (MICS), are the strongest predictors of mortality and signal the urgent need for comprehensive but practical nutrition assessment tools,[13] eg, the Subjective Global Assessment (SGA).

The Malnutrition–Inflammation Score (MIS) is a practical, low cost nutrition assessment tool with a degree of severity score range from 0 (normal) to 30 (severely malnourished) to examine PEW and inflammation. The MIS includes seven components of the SGA, plus body mass index, and serum albumin and transferrin (total iron binding capacity) concentrations (Figure 2). In dialysis patients as well as in kidney transplant patients, and in those with CKD not yet

on dialysis, the outcome-predictability of the MIS is better than its components or laboratory markers of inflammation or other scoring systems such as SGA. The MIS is strongly associated with inflammation, nutritional status, quality of life, and prospective hospitalization and mortality.[12,14,15]

A study by Yamada et al[16] used the MIS as the 'reference standard' to validate five simplified nutrition screening tools in 422 Japanese patients on hemodialysis. The study found the Geriatric Nutritional Risk Index (GNRI) to be the most accurate of the five simplified tools for identifying those patients on maintenance hemodialysis (MHD) who are at nutritional risk. The MIS has been widely used in patients undergoing MHD, and as a reference "gold" standard for assessing other nutrition screening and scoring tools.

In summary, the MIS is a practical tool for clinicians to assess the nutritional status of CKD patients and is a useful metric for risk stratification in MHD patients. The MIS can predict 5-year mortality in MHD patients.[13] Controlled trials of nutrition and anti-inflammatory interventions that can improve MIS are needed to examine the potential of improvement in CKD survival.

Figure 2. Malnutrition Inflammation Score.[12]

Can We Use Blood Biomarkers to Identify Patients Who Benefit from Nutrition Support? (Filomena Gomes, PhD, RD)
Background and aim: Malnutrition is common in the hospital setting and is associated with poor outcomes, yet the underlying pathophysiologic mechanisms and their impact on laboratory parameters are still incompletely understood. Furthermore, there is uncertainty regarding which patients will benefit from intensive nutrition therapy, especially in the polymorbid inpatient population.[17] Blood biomarkers could be a helpful assessment tool for a more personalized approach, to assist in identifying high-risk patients who benefit from nutrition support.

We aimed to explore the association between acute and chronic malnutrition, as assessed by the Nutritional Risk Screening (NRS 2002), with blood biomarkers from different pathophysiological states.

Methods:
This study[18] is a sub-analysis of a prospective observational study, which included consecutive medical inpatients hospitalized through the emergency department of a Swiss tertiary care hospital between February 2013 and October 2013. All patients assessed by the NRS 2002 within 48 hours and with available laboratory values were included in the analysis of this study. Patients were categorized into 3 groups based on NRS scores (NRS <3, NRS =3 and NRS >3), and linear regression analyses were used to explore associations with levels of biomarkers (inflammation/infection, stress, renal function, nutritional status and hematological function) in 3 different models.

Results:
A total of 529 patients with a wide range of diagnoses were included, from which 34% were at risk of malnutrition (NRS ≥3). There were statistically significant differences across groups of malnutrition risk and 9 biomarkers, and the higher the NRS score, the more pronounced the alterations of the biomarkers levels. In a fully adjusted model (for age, gender, comorbidities and main diagnosis), risk of malnutrition was significantly associated with procalcitonin (0.20, 95% CI 0.03–0.37), proadrenomedullin (0.28, 95% CI 0.12–0.43), albumin (–0.39, 95% CI –0.57 to –0.21), copeptin (0.34, 95% CI 0.17–0.51), urea (0.23, 95% CI 0.07–0.38), vitamin D25 (–0.22, 95% CI –0.41 to –0.02), corrected calcium (0.29, 95% CI 0.10–0.49), hemoglobin (–0.27, 95% CI –0.43 to –0.10), and red blood cell distribution width (0.26, 95% CI 0.07–0.44). Subgroup analysis suggested that acute malnutrition, rather than chronic malnutrition, was associated with elevated biomarker levels.

Conclusion
Acute malnutrition was associated with a pronounced inflammatory response and alteration in biomarkers associated with different pathophysiological states. Results from this and other studies suggest that several blood biomarkers correlate with poor nutritional status. However, there is a current lack of interventional data showing that these biomarkers help to identify patients who will benefit from nutrition interventions. Large and good quality interventional studies, eg, the current Swiss multicenter EFFORT study[19] (**E**ffect of Early Nutritional Therapy on **F**railty, **F**unctional **O**utcomes and **R**ecovery of Undernourished Medical Inpatients **T**rial), will help identify candidate biomarkers that associate with positive response to nutrition therapy, with the potential to contribute to better informed decisions for the nutrition care of nutritionally vulnerable patients.

Novel Serum Lipid and Urine Biomarkers of Malnutrition and Inflammation in the Elderly
(Zdeněk Zadák, Prof, MD, PhD)
At present, there are varying views on the interpretation of biomarkers of malnutrition, and there is ongoing research on the mutual influence of nutritional biomarkers during a concurrent inflammatory reaction. The levels of serum proteins can also be reduced during an inflammatory reaction (negative acute phase proteins) with a concurrent rise in inflammatory markers, such as C-reactive protein (CRP, positive acute phase protein).[20,21]

This phenomenon is prioritization of inflammation and malnutrition of the organism. Studies have shown a statistically significant relationship between age, plasma proteins, and positive reactants of inflammation. Revising the interpretation of malnutrition and inflammation, biomarkers reveal the necessity of not using only absolute values of plasma proteins, lipoproteins, and other components, but rather the indices that integrate biomarkers of malnutrition, inflammation, sex, and age.[21,22-24]

Determination of serum proteins still ranks among the principal examinations in malnutrition diagnostics. At present, however, the view of serum proteins as markers only of malnutrition is being challenged, as their levels are affected also during the inflammatory process.

The levels of serum proteins are also decreased in the course of an inflammatory reaction (negative proteins of the acute phase) by the transfer of plasma proteins to the reactants of the acute phase, such as CRP. It is therefore

suitable to examine changes in serum proteins to simultaneously determine CRP, the value of which is increased in inflammation, and to compare the obtained values with each other. A decrease in serum proteins can be also due to transcapillary leak to the interstitial fluid (albumin level is particularly influenced).

Since positive reactants of inflammation (CRP, lipoprotein(a), orosomucoid, and fibrinogen) and biomarkers of malnutrition (albumin, prealbumin, transferrin) are reciprocally dependent, a non-protein and independent biomarker of inflammation is essential for reliable discrimination of both processes. Neopterin, produced by human macrophages after stimulation with interferon gamma, is secreted by activated T-lymphocytes and therefore, is a suitable biomarker to monitor inflammation and immune activation independent of protein catabolism and malnutrition.[25,26] A rational approach is a combination of the various malnutrition and inflammatory biomarkers (Table 1).

Table 1. Biomarkers of Malnutrition and Inflammation

Malnutrition Biomarkers	Inflammation Biomarkers
albumin	C-reactive protein
prealbumin	fibrinogen
transferrin	orosomucoid
cholinesterase	α_1-antitrypsin
retinol-binding protein	neopterin in urine
total protein	sedimentation of erythrocytes
lipids – cholesterol, HDL, LDL and leptin	lipoprotein(a)
some hematological and immunological examinations	arginine depletion
absolute number of lymphocytes, skin tests	

CONCLUSION (Jacqueline Boff, PhD)

Currently, there is insufficient interest among clinicians at large to drive development and validation of a blood biomarker for malnutrition. Compliance with current nutrition screening and assessment tools by clinicians is suboptimal, and likewise, any new screening tool is likely to be underutilized without a sufficient, and perhaps even paradigm-shifting, medical value proposition. Thus, development of novel malnutrition biomarkers needs to embrace clinical practice, drive improved patient outcomes, and add value to current nutrition assessment tools. Biomarkers should change practice, taking into account their cost, availability and reimbursement.

A roundtable consensus identified the need for a panel of biomarkers, as one ultimate biomarker for malnutrition would likely not suffice to buffer against the varied effects of inflammation and other pathologies across patient populations.

For malnutrition risk assessment, clinicians should consider these three parameters: 1) low body mass index (BMI), 2) sarcopenia, and 3) severity of disease state. Participants aligned that these are the most important indicators of malnutrition with today's resources. Whether the target is malnutrition risk assessment or malnutrition diagnosis, patients should be properly coded for malnutrition for appropriate nutrition intervention, and provider reimbursement for treatment and services.

Participants also expressed interest in the use of micronutrient analysis and lean body mass assessment to help screen for and diagnose malnutrition.

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