Guidance for Assessment of the Inflammation Etiologic Criterion for the Global Leadership Initiative (GLIM) on Diagnosis of Malnutrition: A Modified Delphi Approach


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ESPEN Endorsed Recommendation

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1Clinical Nutrition & Metabolism, Uppsala University, Sweden. Theme Inflammation & Ageing, Karolinska University Hospital, Stockholm, Sweden. tommy.cederholm@pubcare.uu.se
2Deans Office and Department of Medicine, Larner College of Medicine, University of Vermont, Burlington, VT, USA. gordon.jensen@med.uvm.edu
3Department of Endocrinology and Nutrition, Complejo Asistencial Universitario de León, Spain. mdballesteros@telefonica.net
4Division of Human Nutrition, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. rb@sun.ac.za
5Food Science Post Graduation Program; Surgery Department, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. isabeldavissoncorreia@gmail.com
6Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain. cuerda.cristina@gmail.com
7Trauma, Critical Care, General & Gastrointestinal Surgery, OhioHealth Grant Medical Center, Columbus, OH, USA. davidevansmd@gmail.com
8Department of Health and Dietetics, Faculty of Health and Medical Science, Teikyo Heisei University, Tokyo Japan. ryojif@med.teikyo-u.ac.jp
9Hunterdon Medical Center, Flemington, NJ, USA. jbochoa@NewSpringhouse.com
10Universidade Federal de Pelotas, Brazil. cristinagbs@hotmail.com
11Department of Gastroenterology and Clinical Nutrition, Hospital Universitaire de Bruxelles, Brussels, Belgium. andre.vangossu@hubruelles.be
12Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada. lg3@ualberta.ca
13Indonesian Central Army Gatot Soebroto Hospital, Jakarta, Indonesia.
hartonoi@gmail.com
14Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana, USA. Steven.Heymsfield@pbrc.edu
15Department of Gastroenterology and Hepatology, Dietetics, Radboud University Medical Center, Nijmegen, The Netherlands, Faculty of Physical Education and Physiotherapy, Department Physiotherapy and Human Anatomy, Research Unit Experimental Anatomy, Vrije Universiteit Brussel, Brussels, Belgium. ha.jager@pl.hanze.nl
16Department of Nutrition and Food Science, International Institute of Health Sciences, Colobo, Sri Lanka. renumajatissa@ymail.com
17Schlegel-UW Research Institute for Aging and Department of Kinesiology and Health Sciences, University of Waterloo, Ontario, Canada. Hkeller@uwaterloo.ca
18American Society for Parenteral and Enteral Nutrition, Columbus, OH, USA, ainsleym@nutritioncare.org
19Critical Care Medicine, Faculty of Medicine, Universidad de la República, Montevideo, Uruguay. wmanzanares@vera.com.uy
20Division of Endocrinology, Metabolism, Diabetes and Nutrition, Mayo Clinic, Rochester, MN. USA. mcmahon.molly@mayo.edu
21Internal Medicine, Clinical Nutrition, Colegio Mexicano de Nutrición Clínica y Terapia Nutricional, México. yolandamendezmx@yahoo.com.mx
22Department of Nutrition, Brigham and Women’s Hospital, Boston, MA, USA. kmogensen@bwh.harvard.edu
23Department of Palliative and Supportive Medicine, Graduate School of Medicine, Aichi Medical University, Japan. nmori@aichi-med-u.ac.jp
Internal Medicine, Sapienza University of Rome, Rome, Italy. maurizio.muscaritoli@uniroma1.it

Hospital Guillermo Almenara EsSalud, Lima Perú. guillermoccnogales@gmail.com

Department of Medicine, Central Clinical School, Monash University, Department of Dietetics, Nutrition and Sport, La Trobe University, Melbourne, Australia. ibolya.nyulasi@monash.edu

Morrison Healthcare, Cleveland, OH. wendyphillips@iammorrison.com

Praxis Kaisereiche - Imperial Oak Outpatient Clinic, Berlin Germany, Endocrinology, Gastroenterology, Clinical Nutrition, Berlin, Germany. matthias.pirlich@googlemail.com

Division of Clinical Nutrition, Department of Medicine, Khon Kaen University, Thailand. pveera@kku.ac.th

Kristianstad University, Kristianstad, Sweden. elisabet.rothenberg@hkr.se

HAN University of Applied Sciences, School of Allied Health; Wageningen University, Division of Human Nutrition and Health, the Netherlands. Marian.devanderSchueren@han.nl

Department of Gastrointestinal Surgery, Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, China. shihp@ccmu.edu.cn

Academy of Nutrition and Dietetics, Cleveland, OH, USA. asteiber@eatright.org

Alpert Medical School of Brown University; Rhode Island Hospital, Surgical Nutrition Service, Providence, RI, USA. mwinkler@lifespan.org

Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy. barazzon@units.it

Department of Biobehavioral Health Science, University of Pennsylvania School of Nursing, and Clinical Nutrition Support Service, Hospital of the University of Pennsylvania, Philadelphia, PA, USA. compherc@upenn.edu

*Tommy Cederholm and Gordon Jensen are co-first authors of this article.
†Charlene Compher and Rocco Barazzoni are co-last authors of this article.
Corresponding author – Tommy Cederholm, M.D., Ph.D., Clinical Nutrition & Metabolism, Uppsala University, Sweden. Theme Inflammation & Ageing, Karolinska University Hospital, Stockholm, Sweden. tommy.cederholm@pubcare.uu.se
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Author Contributions

All authors contributed to the conception and design of the project. Gordon Jensen and Tommy Cederholm led the project from inception to completion. They oversaw the acquisition, analysis, and interpretation of all data. They wrote serial drafts of the
manuscript based upon edits suggested by all authors through multiple rounds of critical
review and revision. All authors agree to be fully accountable for ensuring the integrity
and accuracy of the work and all authors affirm that they have read and approved the
final manuscript.

**Ethical board approval**

Not required for this type of consensus project.

**Permission for use of previously published materials**

Should not be needed. Note that in the supporting information section, cases 1 and 3-5
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**ORCID identifiers**

Maria D. Ballesteros-Pomar [https://orcid.org/0000-0002-5729-9926](https://orcid.org/0000-0002-5729-9926)

Renee Blaaauw [http://orcid.org/0000-0001-7413-5918](http://orcid.org/0000-0001-7413-5918)

Tommy Cederholm [http://orcid.org/0000-0003-3705-0725](http://orcid.org/0000-0003-3705-0725)

Cristina Cuerda [http://orcid.org/0000-0002-07081-622X](http://orcid.org/0000-0002-07081-622X)

M. Isabel T. D. Correia [http://orcid.org/0000-0002-3503-4302](http://orcid.org/0000-0002-3503-4302)

David Evans [http://orcid.org/0000-0001-7366-3567](http://orcid.org/0000-0001-7366-3567)

Ryoji Fukushima [http://orcid.org/0000-0003-4464-664X](http://orcid.org/0000-0003-4464-664X)

Ainsley Malone [http://orcid.org/0000-0001-8345-0303](http://orcid.org/0000-0001-8345-0303)

Kris Mogensen [http://orcid.org/0000-0001-9510-3018](http://orcid.org/0000-0001-9510-3018)
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Abstract

Background & Aims: The Global Leadership Initiative on Malnutrition (GLIM) approach to malnutrition diagnosis is based on assessment of three phenotypic (weight loss, low body mass index, and reduced skeletal muscle mass) and two etiologic (reduced food intake/assimilation and disease burden/inflammation) criteria, with diagnosis confirmed by fulfillment of any combination of at least one phenotypic and at least one etiologic criterion. The original GLIM description provided limited guidance regarding assessment of inflammation and this has been a factor impeding further implementation of the GLIM criteria. We now seek to provide practical guidance for assessment of inflammation in support of the etiologic criterion for inflammation.

Methods: A GLIM-constituted working group with 36 participants developed consensus-based guidance through a modified-Delphi review. A multi-round review and revision process served to develop seven guidance statements.

Results: The final round of review was highly favorable with 99% overall “agree” or “strongly agree” responses. The presence of acute or chronic disease, infection or injury that is usually associated with inflammatory activity may be used to fulfill the GLIM disease burden/inflammation criterion, without the need for laboratory confirmation. However, we recommend that recognition of underlying medical conditions commonly associated with inflammation be supported by C-reactive protein (CRP) measurements when the contribution of inflammatory components is uncertain. Interpretation of CRP requires that consideration be given to the method, reference values, and units (mg/dL or mg/L) for the clinical laboratory that is being used.
Conclusion: Confirmation of inflammation should be guided by clinical judgement based upon underlying diagnosis or condition, clinical signs, or CRP.

KEYWORDS
Malnutrition, inflammation, assessment, C-reactive protein
Introduction

Since the advent of the 21st century, there has been increasing awareness in the medical community of research findings that implicate inflammatory response as an etiologic factor in the development of many medical conditions and their outcomes. Development of treatments that target inflammation has changed paradigms and favorably altered the course of disease. Other diseases, although not of inflammatory origin, may also trigger inflammatory, often systemic, responses.

In the late 20th century knowledge emerged about the role of inflammatory cytokines for catabolism in cancer and some other weight-losing conditions (1-3). This understanding has now been extended to the recognition of inflammation as a key contributor to disease-related malnutrition (4-15). Inflammation may promote anorexia with decreased nutrient intake, altered metabolism with increased muscle catabolism and elevated resting energy expenditure, and blunted response to nutrition interventions (4,10).

Perturbation of micronutrient levels is often observed, including reduced levels of iron, zinc, selenium, vitamin D, and vitamin A (16-23). Severe, sustained or recurrent inflammation promotes increased risk of malnutrition and is associated with adverse outcomes. Negative nitrogen balance may persist despite ongoing nutrition therapy (24). Among patients with a high degree of severe inflammation, i.e., C-reactive protein (CRP) >100mg/L, there was no beneficial effect of nutritional therapy on 30-day mortality (25). Successful management requires treatment of the underlying disease or condition as well as nutrition intervention. Preservation and restoration of muscle mass and function are high priorities. Micronutrient deficiencies should also be addressed. Anti-inflammatory interventions, both medical and nutritional, warrant consideration.
Appreciation of the contributions of inflammation therefore helps to inform assessment of risk of developing malnutrition, supports diagnosis of malnutrition, aids selection of appropriate interventions, provides priority for ongoing monitoring, and guides expected outcomes.

The Global Leadership Initiative on Malnutrition (GLIM) approach to diagnosing malnutrition (13-15), includes recognition of weight loss, low body mass index or reduced muscle mass as phenotypic criteria and the recognition of reduced food intake/assimilation or disease burden/inflammation as etiologic criteria. Fulfillment of at least one phenotypic and at least one etiologic criterion is the requirement for diagnosis of malnutrition. Other approaches include consideration of underlying disease that may serve as a proxy for inflammation; examples include the Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition Indicators to Diagnose Malnutrition (AAIM) (26), Nutritional Risk Screening (NRS)-2002 (27), Subjective Global Assessment (SGA) (28,29) and Patient-Generated Subjective Global Assessment (30). A recent review of GLIM studies in older adults found that a variety of approaches were being used for assessment of inflammation (31); more than half used the diagnosis of inflammatory disease only, whereas the others mainly used CRP alone or combined with the presence of inflammatory disease.

The GLIM priority is to promote a simple global approach that will address the spectrum of healthcare settings where skilled nutrition practitioners and laboratory testing may not be readily available. The original GLIM construct description (13-15) provided limited
guidance as to how to undertake assessment of inflammation in support of malnutrition diagnosis. To address this gap and to assist an array of practitioners in a wide variety of global healthcare settings, we have applied a modified-Delphi approach (32) to develop guidance statements for assessment of inflammation.

Methods

The GLIM core leadership representatives of four major global clinical nutrition societies; the American Society for Parenteral and Enteral Nutrition (ASPEN), the European Society for Clinical Nutrition and Metabolism (ESPEN), the Latin American Federation for Parenteral and Enteral Nutrition (FELANPE), and the Parenteral and Enteral Nutrition Society of Asia (PENSA) appointed a working group of 10 individuals to draft the guidance statements for review. This working group included representatives of each society (Rocco Barazzoni, Renee Blaauw, Cristina Cuerda, Charlene Compher, Isabel Correia, David Evans, Juan Bernardo Ochoa Gautier, and Veeradej Pisprasert) and two co-chairs (Tommy Cederholm and Gordon Jensen). Multiple virtual meetings and email communications were undertaken to review existing approaches and potential recommendations. A PubMed literature search spanning the past 25 years using inflammation and malnutrition as combined search terms revealed 597 citations (last conducted May 10, 2023). Many of these publications were disease- or setting-specific, for example, end-stage renal disease or critical care. However, a more general analysis of a merged data set of geriatric hospitalized patients from across Europe (33), found that food intake was more likely to be significantly compromised at CRP levels above 30 mg/L. Therefore little guidance was available in the context of the more general application to malnutrition diagnosis sought by GLIM,
such that extrapolation of established inflammation assessments from other specific medical conditions proved necessary.

The co-chairs prepared draft guidance statements for review; a modified Delphi approach was then used to ascertain the level of agreement for each statement. An electronic survey was sent to each member of the working group that queried level of agreement on a 5-point scale as “strongly disagree, disagree, indifferent, agree, or strongly agree”. Additional comments and suggestions were also requested. With each round of review, the co-chairs made further edits based upon the feedback received. Transparency was maintained as the feedback and revisions were promptly shared with all participants. The consensus threshold for acceptance of an individual guidance statement was set at 75% agree or strongly agree.

In November 2022 the working group completed an initial review of the draft statements with comments and suggested edits without Delphi scoring. From December 2022 through February 2023, revised versions then underwent three successive rounds of review with further comments and Delphi scoring. With each round, further revision was undertaken with resulting improvements in consensus. For the last round of working group review, the levels of agree or strongly agree exceeded the required threshold for all draft statements (>90% overall).

The co-chairs then constituted an extended review group of experienced physicians and dietitians with expertise in clinical nutrition to bring additional global representation and
expertise to the review process. The 26 members included Ryoji Fukushima, M. Cristina Gonzalez, Andre van Gossum, Leah Gramlich, Joseph Hartono, Steve Heymsfield, Harriet Jager, Renuka Jayatissa, Heather Keller, Ainsley Malone, William Manzanares, Molly McMahon, Yolanda Mendez, Kris Mogensen, Noharu Mori, Maurizio Muscaritoli, Guillermo Contreras Nogales, Ibolya Nyulasi, Wendy Phillips, Matthias Pirlich, Maria Ballesteros-Pomar, Elisabet Rothenberg, Marian de van der Schueren, Han Ping Shi, Alison Steiber, and Marion Winkler. The same modified Delphi approach was undertaken by the extended review group, starting with the draft guidance statements that resulted from the working group review process. Two additional rounds of review, editing, and Delphi scoring were completed by the extended group from February through April 2023. Since additional revisions resulted from the first round of review by the extended group, the working group also participated in the second (final) round of review. Responses for the 36 total Delphi review participants are summarized in the Results.

**Results**

GLIM recommendations for assessment of inflammation using underlying diagnosis, laboratory indicators, and clinical signs.

The final levels of agreement for each guidance statement and noteworthy comments and clarifications that comprise discussion sections for each statement are summarized below. There were 36 total Delphi review participants, so with seven final statements, there were $36 \times 7 = 252$ potential responses. The overall response rate was 100%. Of the responses, 249 were “agree” or “strongly agree” (99%), three were “indifferent”, and
zero were” disagree” or “strongly disagree”. All of the guidance statements readily met the predefined threshold for acceptance.

**Statement 1: Fulfillment of the GLIM disease burden/ inflammation criterion**

The occurrence of acute or chronic disease, infection or injury that is often/usually associated with inflammatory activity may fulfill the GLIM disease burden/inflammation criterion; i.e., confirmation by laboratory markers is not always necessary. This is especially important when such laboratory testing is unavailable. When testing is available, we recommend that laboratory markers be measured in uncertain cases to help confirm the inflammatory character of the underlying disease or condition.

*Agree or strongly agree – 100%.*

**Comments and clarifications on Statement 1**

The GLIM priority (13-15) is to promote a simple global approach that will address the spectrum of healthcare settings where skilled nutrition practitioners and CRP testing are often not available. It is therefore not possible to assume access to such practitioners or to make such laboratory testing a requirement for the guidance that we provide. In the context of the guidance statements, “acute or chronic” categories refer to the duration of the inflammatory disease or condition. The GLIM inflammation criterion does not distinguish between acute and chronic inflammation. Either will fulfil the criterion. The distinction between acute versus chronic inflammation and recognition of the severity of inflammation is helpful in discerning the risk of development and progression of malnutrition, and in guiding interventions and anticipated outcomes (See statements 2
and 3). Uncertain cases would include those where the underlying diagnosis or condition may be suggestive of inflammation, but the clinical setting or signs are inconsistent, such that measurement of CRP may help to clarify inflammatory status. Clinical judgement based upon underlying diagnosis or condition, clinical signs, or laboratory markers should guide confirmation of the presence of inflammatory disease or condition (see Statement 7). Since each individual must still meet a phenotypic criterion (weight loss, low BMI or reduced muscle mass) to receive a diagnosis of malnutrition (13-15), one cannot be diagnosed with malnutrition on the basis of meeting only an etiologic criterion. In general, the GLIM approach has had similar utility in identifying malnourished individuals and in predicting adverse outcomes as other approaches like SGA and AAIM (34-45).

Statement 2: Conditions with severe or moderate acute inflammation

Confirmation of the presence of severe or moderate acute inflammation should be guided by clinical judgement based upon underlying diagnosis or condition, clinical signs, or laboratory markers. The listed conditions are shared as examples that usually have severe acute inflammatory components, thus fulfilling the inflammation criterion. Such conditions include: critical illness, major infection/sepsis, acute respiratory distress syndrome, severe burns, major abdominal surgery, multi-trauma, severe closed head injury, and severe acute pancreatitis. Moderate inflammatory conditions can also present acutely and warrant recognition as described above. Examples would include chronic diseases complicated by acute moderate exacerbations, or acute new presentations with moderate inflammation associated with Crohn’s disease,
rheumatologic conditions, chronic obstructive pulmonary disease (COPD), pancreatitis, diabetes, infections, wounds, and many other examples.

Agree or strongly agree – 100%.

Comments and clarifications on Statement 2

We have defined the “acute” category as rapid in onset and associated with moderate or severe inflammation. We do not include mild inflammatory conditions with the “acute” category as a host of mild infections and other self-limited or easily treated conditions comprise these mild inflammatory states. They should receive appropriate medical treatment and be monitored. If they persist to become chronic or progress to moderate or severe inflammation, then further nutrition evaluation and intervention should be considered. A number of diseases or conditions can fit in either the acute or chronic and mild, moderate or severe inflammation categories depending upon the duration and severity of inflammation that is manifest. Examples are pancreatitis and COPD that are included in both Statements 2 and 3.

Critically ill individuals with severe acute inflammatory conditions like closed head injury, multi-trauma injury, major abdominal surgery or burns, may not initially meet phenotypic GLIM criteria, but such individuals will readily meet the GLIM etiologic criterion for inflammatory condition. A recent prospective cohort study of intensive care patients used low adductor pollicis muscle thickness as an alternative phenotypic indicator of reduced muscle mass and found that use of this measure with the GLIM criteria for diagnosis of malnutrition proved highly feasible and demonstrated high sensitivity,
moderate specificity, and substantial agreement with SGA (45). They should be assumed to be at elevated risk of developing malnutrition and warrant early nutrition intervention and follow up. It must also be noted that a subset of intensive care patients arrives in the surgical and medical intensive care units with preexisting malnutrition. In the critical care setting, practitioners often make use of severity scores like Nutrition Risk in the Critically Ill (NUTRIC) (46) and Sequential Organ Failure Assessment (SOFA) (47) that encompass inflammatory components to help to guide management and expected outcomes.

**Statement 3: Conditions with mild to moderate chronic inflammation**

Confirmation of the presence of mild to moderate chronic inflammation should be guided by clinical judgement based upon underlying diagnosis or condition, clinical signs, or laboratory markers. The conditions listed below are shared as examples that may have mild to moderate chronic inflammatory components i.e., clinical findings or laboratory markers that fulfill the disease burden/inflammation criterion. Examples of such chronic conditions include: congestive heart failure, cystic fibrosis, COPD, Crohn’s disease, celiac disease, rheumatoid arthritis, diabetes, abdominal obesity, metabolic syndrome, malignancies, infections like tuberculosis, HIV/AIDS, pressure wounds, periodontal disease, chronic kidney disease, hepatic cirrhosis, mild/moderate pancreatitis, organ failure/transplant, and many other examples. It is important to recognize that inflammation may remit, relapse or be exacerbated, depending upon the course of disease, treatment modalities or superimposed events or complications.

*Agree or strongly agree – 100%.*
Comments and clarifications on Statement 3

This statement is not intended to provide a comprehensive list of chronic inflammatory conditions, but rather to provide relevant examples. We deliberately encompass both mild and moderate chronic inflammatory conditions in statement 3, and do not suggest that all the highlighted examples have the same degree of inflammation. The “chronic” category is characterized by mild to moderate inflammation of at least 2-4 weeks duration. We do not generally include severe inflammatory conditions with the “chronic” category, but there are overlapping conditions like “chronic critical illness” associated with Persistent Inflammation, Immunosuppression and Catabolism Syndrome (48) that may be reasonably assigned to the chronic category based upon duration, severity of inflammation, and clinical judgement. This type of protracted severe inflammation is often associated with a deteriorating course and poor outcomes. These patients effectively remain in the acute inflammatory state and are at extremely high risk to develop severe malnutrition and warrant ongoing nutrition intervention and monitoring.

An individual is not required to have laboratory documentation of active inflammation to meet the GLIM inflammation etiologic criterion. For example, a Crohn’s disease patient with a mild acute mucosal relapse may not have an elevated CRP, but the patient will have a chronic condition that is associated with bouts of inflammation and will therefore satisfy the GLIM etiologic inflammation criterion. An individual does not have to have active inflammation for a disease or condition to contribute to malnutrition. First, it is common for a recent bout of inflammation that has resolved to have contributed to
ongoing malnutrition. Second, as well illustrated by Crohn’s disease and COPD, there are a variety of chronic diseases or conditions in which inflammation may reoccur. Third, we can make a direct connection to disease-related malnutrition, as other disease-related mechanisms besides inflammation contribute to malnutrition (see Statement 4). It is important to recognize all such diseases or conditions whether active inflammation is present or not. It must also be highlighted that GLIM determines malnutrition severity based only on the phenotypic criteria of weight loss, low BMI or reduced muscle mass, not the etiologic criteria of disease burden/inflammation or reduced food intake or assimilation (13-15).

Statement 4: Conditions with no clear or perceptible inflammation

Disease conditions that have no clear or perceptible inflammatory components will not fulfill the disease burden/inflammation criterion unless confirmed by laboratory analyses. Typical examples that often result in malnutrition include psychiatric diagnoses like anorexia nervosa and depression; select malabsorptive, obstructive or dysmotility conditions like esophageal stricture, anatomic short bowel syndrome; and intestinal pseudo-obstruction; and neurological conditions like dysphagia after cerebrovascular accident. To highlight the distinction, we note that there are non-disease conditions that are associated with limited resources or environment that compromise food security, access, or intake, including poverty, famine, and war. These conditions also lack inflammatory components and often result in malnutrition. Starvation may also be complicated by recurrent infections that contribute to malnutrition. Note that malnourished individuals with conditions that have no clear or perceptible inflammatory
components can be readily diagnosed with malnutrition based upon the GLIM phenotypic criteria and meeting reduced food intake or assimilation as an etiology.

**Agree or strongly agree – 100%.

Comments and clarifications on Statement 4

Among those conditions with no clear or perceptible inflammatory components there are select malabsorption and dysmotility conditions like esophageal stricture, bariatric surgery complications, anatomic short bowel syndrome, and intestinal pseudo-obstruction. These conditions will generally meet the GLIM etiologic criterion of impaired nutrient intake and assimilation. They can however be complicated by inflammatory conditions like aspiration, bacterial overgrowth or hepatic dysfunction.

We are aware that it has been reported that anorexia nervosa may be associated with altered cytokines levels and neuro-inflammation (49,50). However, CRP is generally not elevated and albumin does not typically decrease in patients with anorexia nervosa until there is life-threatening malnutrition or a superimposed inflammatory event (51-53).

**Statement 5: Laboratory markers indicating inflammation**

The documentation of laboratory markers indicating inflammation may support confirmation of the disease burden/inflammation criterion. Use of CRP is recommended and alternative laboratories are noted in the comments and clarifications section below.

Due consideration of the clinical setting and known limitations of these markers must be given.
Agree or strongly agree – 100%.

Comments and clarifications on Statement 5

CRP has a half-life of 19 hours and therefore suffers limitations as a relatively brief point in time measure (64). CRP is a positive acute phase reactant synthesized by the liver, so levels may be reduced in advanced liver disease. In contrast, end stage kidney disease is associated with increased CRP levels that may be elevated due to inflammation and decreased filtration. Use of nonsteroidal anti-inflammatory drugs, magnesium supplements or statins may lower CRP levels (55-57). It should also be recognized that CRP and other inflammatory indicators may be reduced in patients with immunosuppressive conditions or therapies. Such patients may not meet the inflammation criterion, but they should be evaluated for the reduced food intake or assimilation etiologic criterion and associated phenotypic malnutrition criteria.

Alternative laboratory measures offer potential as inflammatory indicators, but concerns regarding sensitivity, specificity, availability, cost, and need for more extensive testing and validation apply to these measures in varying degrees. Alternative indicators of inflammation include interleukin-6, erythrocyte sedimentation rate, neutrophil/lymphocyte ratio, T lymphocyte counts (CD3 +), thrombocytosis, myeloid derived suppressor cells, albumin, albumin/CRP ratio, procalcitonin, red cell distribution width, nucleated red blood cells, hyperglycemia, hyperinsulinemia, HOMA calculation, iron kinetics (Fe, ferritin, and transferrin), lactate, fibrinogen, and calprotectin (for inflammatory bowel disorders). Gene polymorphisms may be associated with more
robust inflammatory response (58,59). Systemic inflammatory response has also been associated with distinctive gene expression arrays (59-61). "Omics" approaches including genomics and metabolic phenotyping, offer promise for early recognition of individual risk for severe inflammatory response (62-64).

There has been growing interest in the use of albumin as a proxy indicator of inflammatory activity. It is a negative acute phase reactant that declines precipitously in severe inflammatory states. Long felt to be an indicator of malnutrition, strong consensus now suggests that albumin lacks validity for the diagnosis of malnutrition in the setting of inflammatory conditions (65). Inflammation promotes decreased serum albumin by reprioritization of hepatic protein synthesis and redistribution of serum proteins through increased capillary permeability. With a half-life of 3 weeks, serum albumin levels recover slowly as inflammation abates, but it offers the advantage of being widely available as part of routine hospital admission laboratory profiles across the globe. Some practitioners combine interpretation of albumin levels with CRP testing, such that if albumin is low and CRP is elevated, it is highly likely that inflammatory activity is manifest. Despite the well-documented limitations of using albumin as an indicator of malnutrition, there remains value in measuring albumin due to its utility as an indicator of inflammation and it serves as a potent predictor of adverse patient outcomes.

Statement 6: Application of CRP testing

It is recommended that the recognition of underlying medical conditions commonly associated with inflammation be supported by CRP measurements when the
contribution of inflammatory components is uncertain. For **acute conditions**, CRP levels ≥10 times higher than the upper reference value for the methodology of the selected clinical laboratory can be used to support the presence of moderate to severe acute inflammation. For example, CRP levels of 10-50 mg/L may be used to meet the acute criterion at a moderate level of inflammation, but CRP levels greater than 50 mg/L support severe acute inflammation. Since critically ill patients vary in their degree of inflammation, measurement of CRP is helpful to ascertain its severity (45). For **chronic conditions**, serial measures of CRP higher than the upper reference value for the methodology of the selected clinical laboratory support the presence of the chronic inflammation criterion. For example, serial measures of elevated CRP at 3.0-9.9 mg/L and 10-50 mg/L may be used to support mild and moderate inflammation, respectively.

*Agree or strongly agree – 94%.*

**Comments and clarifications on Statement 6**

To interpret CRP values, consideration should be given to the methodology, reference values, and units (mg/dL or mg/L) for the clinical laboratory that is being used (66). A conversion factor of 10-fold may be used to go from mg/dL to mg/L and the accuracy of that conversion should be confirmed. Standard assays detect CRP levels of 10 mg/L or greater, while high sensitivity assays reliably detect CRP levels of 0.5 to 10 mg/L (67). Standard low sensitivity CRP assays are suitable for many routine clinical surveillance applications. Assessment of conditions that require detection of lower CRP levels warrant use of high sensitivity assays. For example, increased risk of cardiovascular disease may be detected at levels as low as 1.0-3.0 mg/L (68). Laboratory standards
and recommended thresholds for assignment of severity vary (69), but for simplicity, we propose that CRP levels of 3.0-9.9 mg/L are consistent with mild inflammation, levels of 10-50 mg/L are consistent with moderate inflammation, and levels greater than 50 mg/L are consistent with severe inflammation. These thresholds are provided to help support identification of individuals with inflammatory diseases and conditions, not to assess risk for development of disease. They are consistent with reports that moderate and severe inflammation may be associated with significant reductions in food intake in hospitalized older patients (33).

Serial CRP measures can be helpful when the status or contribution of inflammation is unclear in the setting of a chronic condition. This approach is used routinely in the medical management of cardiovascular disease, COPD, Crohn’s disease, and rheumatologic conditions. Measurement of CRP trends can be helpful, because a single normal CRP value does not exclude the possible contribution of an inflammatory component. Whenever possible, the opportunity to make use of CRP test results that have been ordered for other medical purposes is encouraged.

**Statement 7: Application of clinical judgement**

Clinical judgement based upon integration of underlying diagnosis or condition, clinical signs, and/or laboratory markers should guide confirmation of the presence of inflammatory disease or condition. The sound interpretation of some of these indicators requires clinical training and expertise. The presence of clinical inflammatory symptoms and signs, like fever and leukocytosis, can support the presence of inflammatory
activity. Judgement is also indicated to discern when serial CRP measurements may be indicated or when alternative laboratory indicators of inflammation warrant consideration (see statement 5). While some of these indicators may suffer limited sensitivity and specificity, they can still be used by clinicians to support the potential presence of inflammation.

*Agree or strongly agree – 97%.*

**Comments and clarifications on Statement 7**

Interdisciplinary collaboration with experienced clinicians is encouraged. Development of clinical training workshops that are focused upon assessment of inflammation in relation to malnutrition for practitioners with limited training or experience is warranted.

**Conclusion**

Inflammation is widely recognized as a contributor to disease-related malnutrition (4,10). However, limited guidance as to how to undertake assessment of inflammation in support of malnutrition diagnosis and treatment has been available. In this report, we describe use of a modified-Delphi approach to develop guidance statements for assessment of inflammation. The resulting guidance statements secured strong overall support with 99% of the responses by the Delphi participants being either “agree” or “strongly agree”. This guidance has been developed for use with the GLIM approach to diagnose malnutrition, but it should also be helpful for healthcare practitioners that use other approaches for malnutrition diagnosis.
Key practical guidance points for the clinician may be summarized as follows. The occurrence of acute or chronic disease, infection or injury that is often/usually associated with inflammatory activity may fulfill the GLIM disease burden/inflammation criterion. When testing is available, CRP should be measured in uncertain cases to help confirm the inflammatory character of the underlying disease or condition. Confirmation of inflammation should be guided by clinical judgement based upon underlying diagnosis or condition, clinical signs, or CRP. Disease conditions that have no clear or perceptible inflammatory components will not fulfill the disease burden/inflammation criterion unless confirmed by CRP.

To promote adoption of the proposed guidance, dissemination with translation into other languages will be necessary. Priority should also be given to developing the contents for a clinical training workshop focused upon assessment of inflammation in relation to malnutrition that can be widely shared with practitioners with limited training or experience. We anticipate that the guidance statements will continue to evolve over time, as new research breakthroughs target priorities to develop better biomarkers of inflammation as well as better understanding of the complex interactions of inflammation and malnutrition. “Omics” approaches, including genomics and metabolic phenotyping, may ultimately facilitate individualized assessment of inflammatory risk to promote personalized treatment and care.
Supplementary Material

Additional supporting case presentations may be found online in the Supporting Information section at the end of the article.
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Supplementary Material

Case presentations that illustrate assessment of inflammation.

Cases 1 and 3-5 have been adapted from Jensen GL, Hsiao PY, Wheeler D. Adult nutrition assessment tutorial. JPEN J Parenter Enteral Nutr 2012;36:267-274.

1. Moderate chronic inflammation – Advanced chronic liver disease/cirrhosis

A 52-year-old male presented for a follow up clinic appointment with an established history of cirrhosis and portal hypertension in the setting of long-term ethanol abuse. He had gained approximately 4.5 kg over the prior two weeks and exhibited massive ascites. Additional findings included mild encephalopathy (grade 1) with poor concentration, asterixis, and scleral icterus. A family member reported that his food intake had been severely compromised for weeks. At presentation the patient weighed 73 kg and was 173 cm in height (BMI 24.4 kg/m^2).

The medical record revealed that 10 years previously his weight was 75 kg (BMI 25.1 kg/m^2), whereas a more recent weight recorded one year ago without ascites was 65 kg (BMI of 21.7 kg/m^2). He was afebrile. Laboratories included total bilirubin 3.8 mg/dL, aspartate aminotransferase 96 IU/L, alanine aminotransferase 111 U/L, alkaline phosphatase 162 IU/L, albumin 1.7g/dL, prothrombin time 18 seconds, CRP 27 mg/L, and prealbumin 6.8 mg/dL. Physical findings were notable for ascites and extensive loss of muscle and subcutaneous fat.

**Diagnosis** - Advanced liver disease with cirrhosis and moderate inflammatory response.

This patient meets the GLIM malnutrition etiologic criteria for inflammation and reduced food intake, and meets GLIM phenotypic criteria for severe malnutrition, specifically loss
of muscle mass. This patient would also likely meet underweight and weight loss criteria were it not for the manifest ascites. Note that CRP, albumin, and prealbumin are not reliable indicators in the setting of advanced liver disease, so underlying diagnosis and clinical judgement are used to support the presence of moderate inflammation.

2. Low-moderate chronic and relapsing inflammation – Chronic obstructive pulmonary disease

A 78-year-old male was evaluated when he made a regular visit at the outpatient clinic. His history revealed that he had smoked about one pack per day from early adulthood until he ceased smoking 5 years before. At age 50 years, he was diagnosed with chronic bronchitis due to chronic productive coughing. At age 60 years, he was diagnosed with COPD due to characteristic respiratory distress with confirmatory spirometric assessment and radiologic examination. Over the past 10 years, he suffered approximately three recurrent COPD exacerbations annually with fever, worsened respiratory distress and cough productive of colored sputum that usually required antibiotic treatment, and sometimes hospitalization. At 50-years his weight was 85 kg and height was 178 cm (BMI 26.9 kg/m²). At the outpatient visit his weight was 62 kg and height 175 cm (BMI 20.2 kg/m²). Weight loss was 23 kg (27%). Reduced appetite and low food intake were notable, especially during the exacerbations. A calf circumference of 28 cm and low handgrip strength were consistent with sarcopenia (70-71).

Diagnosis: COPD with chronic/relapsing inflammation. In this case no laboratory confirmation is needed to fulfill the inflammation etiologic criterion of malnutrition,
although there were numerous CRP measurements performed that were usually in the range of 5-70 mg/L. Accessible data are enough to establish the diagnosis of severe malnutrition according to the GLIM concept (weight loss, underweight, low muscle mass, inflammation and reduced food intake).

3. Moderate chronic inflammation - Metabolic syndrome and sarcopenic obesity

A 70-year-old female presented for a follow up clinic appointment with longstanding obesity and metabolic syndrome. She had been receiving medications that included a statin, a diabetes oral agent, and a non-steroidal anti-inflammatory for her hypercholesterolemia, diabetes mellitus, and painful destructive joint disease of the knees, respectively. Her chief complaint was worsening limitations in function that included compromised mobility. She lived in her own home and was effectively housebound. She reported limited financial resources and difficulty obtaining regular meals. She indicated that she may have lost some 5-10 kg over the past 6-months without trying to lose weight. An adult daughter reported that meals that she left for her mother were frequently left in the refrigerator, uneaten. Upon evaluation, her weight was 85 kg and height was 158 cm (BMI 34 kg/m²). Prior records confirmed a 10 kg weight loss compared to her last visit 6 months before. Laboratories included fasting glucose 7.2 mmol/L (130 mg/dL), HbA1c 7.0%, cholesterol 4.7 mmol/L (180 mg/dL), HDL-cholesterol 1.2 mmol/L (45 mg/dL), triglyceride 1.4 mmol/L (125 mg/dL), albumin 41 g/L (4.1 g/dL), and CRP 35 mg/L. Physical examination revealed truncal adiposity with waist circumference of 96 cm. She had difficulty arising from a chair and ambulating with evidence of generalized loss of strength and knee discomfort.
Diagnosis – Metabolic syndrome and sarcopenic obesity with moderate inflammation. The patient meets the GLIM malnutrition etiologic criteria for inflammation and reduced food intake, and meets GLIM phenotypic criteria for mild to moderate malnutrition based upon weight loss and likely reduced muscle mass. Sarcopenia is also likely in view of observed functional impairment (72). Even though loss of muscle strength was observed, physical performance and strength testing would be helpful, and the loss of muscle mass would be difficult to appreciate without using other body composition methods for confirmation. While mild to moderate inflammation may be inferred based upon underlying diagnoses and clinical judgement, the complexities of managing this case warrant periodic monitoring of CRP.

4. Severe acute inflammation – Multi-trauma

A 38-year-old male suffered multi-trauma secondary to a motor vehicle accident. His injuries included ruptured spleen, Grade III liver laceration, left femur fracture, and bilateral pulmonary contusions. He is status post damage control celiotomy, splenectomy, and packing of the liver. He was transferred to the Trauma Intensive Care Unit on a ventilator where he continued to be resuscitated. Post-surgery day 2 of admission this patient had temperature 39°C, heart rate 98 beats per min, respiratory rate 26 breaths per minute, and pCO₂ 28mmHg. He was markedly edematous with weight gain of 6.8 kg above his usual body weight. His open abdomen was dressed. Laboratories consistent with active inflammation included white blood cell count 25,000/mm³, CRP 180 mg/L, albumin 2.6 g/dL, and prealbumin 11.0 mg/dL. He was reported to have been well-nourished with suitable dietary intake prior to his injury, but his dietary intake is anticipated to be compromised for a week or greater.
Diagnosis - Multi-trauma consistent with severe acute systemic inflammatory response. The patient meets the GLIM etiologic criterion for inflammation and while not currently meeting any GLIM phenotypic malnutrition criteria, warrants early nutrition intervention in view of high risk to develop malnutrition. Note that in this case, it would have been possible to assume the presence of severe acute inflammation on the basis of underlying diagnosis and clinical judgement without CRP measurement. However, in the management of critically ill patients, it is useful to measure CRP levels over time in order to discern the severity of inflammation.

5. No clear or perceptible inflammation – Anorexia nervosa

A 26-year-old female was admitted to the hospital with a diagnosis of anorexia nervosa and a longstanding history of restrictive eating behavior without purging. She had lost one-third of her body weight over 6-months. Upon admission the patient weighed 37.2 kg and was 167.6 cm in height (BMI of 13.2 kg/m²). Her resting heart rate was 50 beats per minute. She was afebrile. Laboratory values included: CRP 0.7 mg/L, albumin 4.0 g/dL, and prealbumin 25 mg/dL. She exhibited generalized loss of muscle and subcutaneous fat. Marked underweight status was evident with weight loss of 19.1 kg over 6-months. Mid-arm muscle circumference measurement was below the 5th percentile.

Diagnosis - Anorexia nervosa with no clear or perceptible inflammation. This patient meets the GLIM etiologic criterion for reduced food intake and meets GLIM phenotypic criteria for severe malnutrition based upon weight loss, low BMI, and reduced muscle mass. It is therefore reasonable to assign this patient to the category of disease related malnutrition with no perceptible inflammation due to restricted intake on the basis of underlying diagnosis and clinical judgement. One should however be vigilant for any
superimposed inflammatory complication, which could be of catastrophic consequence in someone with this degree of malnutrition.
Conflict of Interest Statement

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