Review Article

"The Big Three" of geriatrics: A review of perioperative cognitive impairment, frailty and malnutrition

ABSTRACT

Cognitive impairment, frailty, and malnutrition are three of the most impactful pathologies facing an aging population, having dramatic effects on morbidity and mortality across nearly all facets of medical care and intervention. By 2050, the World Health Organization estimates that the population of individuals over the age of sixty worldwide will nearly double, and the public health toll of these demographic changes cannot be understated. With these changing demographics comes a need for a sharpened focus on the care and management of this vulnerable population. The average patient presenting for surgery is getting older, and this necessitates that clinicians understand the implications of these pathologies for both their immediate medical care needs and for appropriate procedural selection and prognostication of surgical outcomes. We believe it is incumbent on clinicians to consider the frailty, nutritional status, and cognitive function of each individual patient when offering a surgical intervention, as well as consider interventions that may delay the progression of these pathologies. Unfortunately, despite excellent evidence supporting things like routine pre-operative frailty screening and nutritional optimization, many interventions that would specifically benefit this population still have not been integrated into routine practice. In this review, we will synthesize the existing literature on these topics to provide a pragmatic approach and understanding for anesthesiologists and intensivists faced with this complex population.

Key words: Cognitive impairment, delirium postop, frailty, geriatric anesthesia, malnutrition, neurocognitive disorder, nutrition

Introduction

The geriatric population is one of the fastest growing segments of the population worldwide. In 1920, less than one in 20 people in the United States were age 65 and over, while in 2020 this proportion grew to one in six. The same population includes 40% of the surgeries in the US.[1] Similarly, the population of Saudi Arabia grew from a mere 6,167,308 in 1974 to 27,136,977 in 2010: with the population of residents over the age of 65 growing from 254,937 to 678,731 during this period.[2] Aging is associated with a progressive loss of functional reserve in all organ systems and an increased vulnerability to acute stressors. This decrease in reserve with aging that leaves a person less capable of responding to a stressor has been termed "homeostenosis." Mortality is considerably elevated among older persons who are frail or who have probable dementia, highlighting the prognostic value of geriatric conditions for outcomes following major surgery.[3] The first step on this journey is likely to identify

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the patients who are frail and have preexisting cognitive dysfunction or malnutrition. Though at this time, many risk factors are not modifiable, and things such as assessing for frailty, optimizing nutrition, and employing strategies to prevent postoperative delirium (POD) should be considered.

In this manuscript, we will address three of the most important issues facing the geriatric surgical population, cognitive impairment, nutrition, and frailty. We will review the most recent literature together in a pragmatic approach to help the anesthesiologists and intensivists better manage this fragile population.

Cognitive Impairment

The elderly population is more vulnerable to the impact of surgery and anesthesia on the brain. POD is associated with an increased risk of perioperative and long-term mortality,[4,5] as well as potentially leading to early and long-term cognitive decline, and new onset dementia.[6,7] To minimize this impact and optimize cognitive recovery and perioperative experience, the Perioperative Brain Health Initiative (BHI) was founded in 2015 and has been one of the American Society of Anesthesiologists (ASA) primary missions ever since.

Postoperative cognitive decline after anesthesia and surgery can have a wide spectrum of manifestations and can vary significantly in duration. In the past, these various presentations were all classified under the term "postoperative cognitive decline or POCD." This term was imprecise and did not include a subjective component. On October 16, 2018, six major medical journals simultaneously published the results of a multidisciplinary, international team that worked on a more specific nomenclature, aligned with the Diagnostic and Statistical Manual 5th edition (DSM-V) and National Institute for Aging and the Alzheimer Association (NIA-AA) definitions.[8] The term perioperative neurocognitive disorder (PND) was chosen to describe alterations in behavior, affect, and cognition that occasionally occur after anesthesia and surgery. The PND as an umbrella covers POD, delayed neurocognitive recovery (dNCR), and major or minor neurocognitive decline (NCD) postoperatively. This new term can be summarized as Figure 1:

1. Preexisting cognitive impairment diagnosed in the pre-operative period.
2. Postoperative persistent or recurrent delirium (beyond the transient "emergence" from general anesthesia) and takes specifier "postoperative" if new onset within 7 days of anesthesia and surgery.
3. DNCR: the cognitive decline not due to delirium and diagnosed up to 30 days after a procedure.

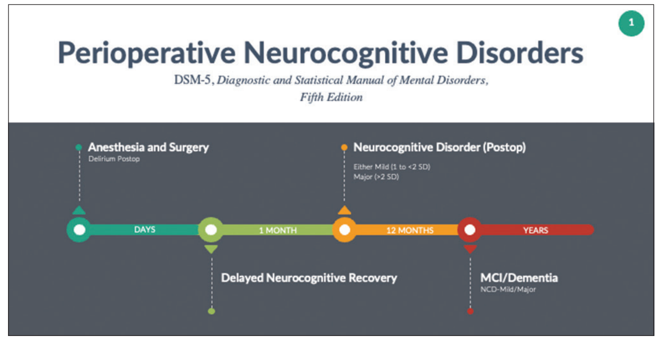

Figure 1: Perioperative neurocognitive disorders

4. Major or minor NCD that persists or is diagnosed up to 12 months after the procedure (termed NCD [postoperative]). The mild form has symptoms roughly equivalent to the NIA/AA term mild cognitive impairment. The major form has symptoms roughly equivalent to the NIA/AA definition for dementia.

The risk factors for PND are composed of both predisposing and precipitant factors. The most common predisposing factors are age, dementia, frailty, male gender, poor vision and hearing, sleep disturbances, and mild cognitive impairment. Precipitating factors include surgery, anesthesia, hypoxia, untreated pain, sepsis, acute illness, an acute exacerbation of chronic illness, and polypharmacy. The latter includes psychoactive medications such as benzodiazepines, antihistamines, antipsychotics, phenothiazines, or anticholinergic drugs. In 2019, the American Geriatric Society (AGS) has published a list of potentially inappropriate medications for the elderly population.[9] The pathophysiology of the neurocognitive disorder is complex and not well understood. Some previously identified factors are inflammation, decreased acetylcholine, increased dopamine activity, sleep disturbances, and nervous system glymphatic function disorder. A recently published meta-analysis on the impact of age on perioperative inflammatory biomarkers, which included 45 studies, showed that in both cardiac and non-cardiac studies, older patients had higher pre-operative levels of interleukin (IL)-6 and C-reactive protein (CRP) and higher postoperative levels of IL-6 than younger patients.[10]

About a quarter of patients older than 65 have some cognitive impairment pre-operatively. These patients are more prone to develop PND postoperatively. This is associated with the development of delirium postoperatively, a longer hospital stay, and a lower likelihood of going home upon hospital discharge.[11,12] Frailty and cognitive screening were recommended by the American College of Surgeons and the American Geriatrics Society in their 2012 jointly published guidelines. A recent consensus statement recommended a pragmatic pre-operative assessment to risk-stratify patients.[13] The screening tools, such as the Mini-Cog, the Mini-Mental State Examination (MMSE), or the Montreal Cognitive Assessment (MoCA), are fast and practical in the pre-operative setting.[14-17] For even more simple and quicker assessments, tests such as the clock-drawing test and the verbal fluency test have also been suggested.[16] The University of Florida group published a manuscript where they suggest that cognitive and frail assessment pre-operatively was feasible and the benefits in identifying frail or cognitive impairment made the challenges minimal.[18]

One of the modifiable risk factors to prevent postop delirium and neurocognitive disorder is titrating anesthetics based on EEG monitoring. This was recommended as part of best practices for postoperative brain health by the fifth international perioperative neurotoxicity working group.[19] Elderly patients could be more deeply unconscious than are normally required for general anesthesia. They are up to 10 times more likely to be in a state of burst suppression than younger patients, a pathological phenomenon that should be avoided. In addition, there is abundant literature linking it to poor cognitive outcomes after surgery.[20,21] Power across all frequency bands decreases significantly with age for both propofol and sevoflurane; elderly patients show EEG oscillations ~ two- to threefold smaller in amplitude than younger adults. In the elderly compared with young patients, alpha power decreases more than slow power, and alpha coherence and peak frequency are significantly lower.[22] Given this, lower intraoperative frontal alpha power could be used as a physiological marker to identify older adults with lower pre-operative cognitive function.[23]

The balanced anesthesia delirium study was a 515-patient sub-study of a 6644-patient international trial investigating the impact of anesthetic depth on one-year mortality, and it randomized the patients to a bispectral index (BIS) target of 35 vs 50. This sub-study found that targeting BIS readings of 35 resulted in a significantly higher ($P = 0.010$) incidence of postoperative delirium compared with targeting BIS readings of 50 (28% vs 19%). This was in contrast to the previous large trial, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Symptoms (ENGAGES), that randomized the patients to a BIS guided vs standard of care. However, in ENGAGES, the BIS-guided group received only 0.11 minimum alveolar concentration (MAC) less anesthetic than the standard group, which may not have been a large enough difference to demonstrate the clinical effect. It is interesting to note that patients with deeper EEG indices had more episodes of postoperative delirium.[24,25]

It should be mentioned that the processed EEG index number such as BIS is not ideal to monitor anesthetic dosage for two reasons: It has a non-linear relationship with anesthetic dosage in adults of all ages, and it could paradoxically increase with age even with higher doses of inhaled anesthetic.[26] Age adjusted MAC should be used for all patients and more importantly in elderly population. In practice particularly in community hospital, the adjustments may be lower than what is needed and therefore represent an overall increase in “age-adjusted dose” as patients grow older.[27] Using processed EEG becomes even more important in decreasing delirium in total intravenous anesthesia (TIVA) and in MAC cases with regional anesthesia.[28] The current data are conflicting, and the studies are not well done to adequately address the difference between regional and general anesthesia for POCD and POD.[29,30]

Another important issue is to assure that consent for surgery is properly informed, and the risk of PND (e.g., confusion, inattention, and/or memory problems) should be discussed with older patients and their families.[19,31,32] There are some new studies regarding “cognitive rehabilitation” that will be addressed elsewhere in this volume.

Frailty

Frailty can broadly be defined as a clinical syndrome characterized by an overall loss of functional reserve resulting from an accumulation of age and disease-related impairments.[33,34] This definition has often been further divided into physical frailty (defined by objective measures like grip strength, walking speed, fatigue, weight loss) and deficit accumulation frailty. The prevalence of frailty varies widely by the tool used for definition and the population that is studied but has been described as occurring at a rate of 4–16.2% in patients over the age of 65.[34-36] Pre-frailty, which is when a patient meets some but not all criteria, is dramatically more prevalent in this same population. Notably, old age in isolation is not sufficient to define frailty. Frailty has been consistently demonstrated to predict mortality across both age and gender.[35,37] Further, frail patients are particularly vulnerable to adverse outcomes following surgical procedures, and across numerous investigations, frailty has been associated with robust increases in both morbidity, mortality,[33] and cognitive dysfunction in cardiac patients.[38] Many different frailty measures have been developed over the years to better quantify this condition and to provide a means of risk stratification in this population. These assessments of frailty have ranged from those gathered solely from electronic medical records or registries to comprehensive geriatric assessments,[39] individual laboratory tests,[40,41] direct physical measures like gait speed and hand grip strength, and a variety of different composite scores/questionnaires like the Fried Phenotype,[34] Edmonton Frail Scale (EFS),[39] and clinical frailty scale (CFS).[42]

Unfortunately, despite excellent data suggesting the predictive value of perioperative frailty assessment, its incorporation into routine practice has been variable.[43,44] Frequently cited barriers include issues related to general feasibility such as ease of assessment, complexity of questions, time required to complete, and requirement for specialized equipment in the case of certain physical measures. Additionally, the timing of these assessments must be considered. The real value of these assessments may be in avoiding elective procedures in particularly high-risk patients. This of course can only be accomplished well if frailty is considered well before the day of scheduled surgery. Each of the different tools that has been developed for frailty assessment has benefits and drawbacks, but three of the most studied have been the FP, CFS, and EFS.

The Fried Phenotype (FP), also known as the "Frailty Phenotype" or "Fried Frailty Tool," was originally described by Fried *et al*.[34] in 2001 and intended to serve as a more functional method for assessing frailty. In simplified terms, Fried defined frailty as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Notably, each of these individual components has more detailed criteria, cutoff values, and definitions for meeting the diagnosis of frailty. Initially, FP was defined for the general assessment of frailty but subsequently has been extensively studied specifically in surgical populations.[33,34,36,45] On a recent meta-analysis, FP was robustly associated with both mortality (odds ratio, 3.95; 95% CI, 2.00 to 7.81; $P < 0.0001$), complications (odds ratio, 2.47; 95% CI, 2.00 to 3.04; $P < 0.0001$), and delirium (odds ratio, 3.79; 95% CI, 1.75 to 8.22; $P = 0.001$) following surgical procedures.[33] Despite these associations, FP is often not incorporated into clinical practice as it requires specialized equipment for assessing grip strength and walking speed.

Unlike the relatively complex FP, the Edmonton Frail Scale is a questionnaire that can be administered by a layperson without medical training. The EFS evaluates ten domains including cognition, general health, functional independence, social support, medication use, nutrition, mood, continence, and functional performance, ultimately offering a score on a 17-point maximum scale.[46] Though many studies have been published using the EFS, on meta-analysis, there was insufficient data to comment on its association with mortality, but the EFS was significantly associated with both complications (odds ratio, 2.92; 95% CI, 1.52 to 3.46; $P = 0.001$) and delirium (odds ratio, 2.11; 95% CI, 1.06 to 4.21; $P = 0.034$).[33] In this same analysis, EFS was found to be weakly predictive of both complications and mortality.

The CFS, developed at Dalhousie University, is a judgment-based frailty scoring tool that functions without a questionnaire or specific physical testing. The CFS instead offers a simplified chart, scoring frailty from 1 to 9, with 1 being a very fit individual to 9 being a terminally ill patient [Figure 2]. Each subsection offers an overall picture of a patient who would meet the frailty score and allows clinicians to make a judgment call when placing a patient in a particular score. Due to this very simple design, the CFS has largely been considered one of the most feasible tools in clinical practice.[33,47] Based on a 2020 meta-analysis, the CFS was clearly associated with increased mortality (odds ratio, 4.89; 95% CI, 1.83 to 13.05; $P = 0.002$) and, in fact, had the

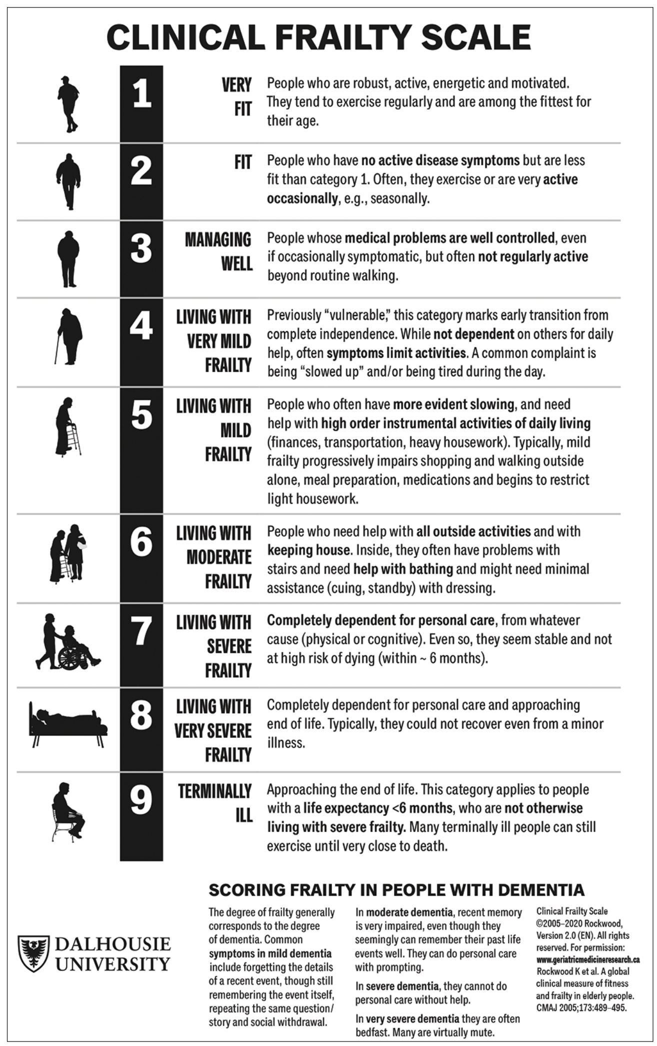

Figure 2: Clinical frailty scale

largest effect size of any instrument that was evaluated, but interestingly did not reach significance when association with complications (odds ratio, 1.68; 95% CI, 0.95 to 2.95; $P = 0.073$). This may be partially attributable to a much larger number of patients evaluated specifically for mortality versus complications (n = 7,793 vs 519). Of the discussed frailty assessments, the CFS appears to have the fewest documented issues with feasibility.[33,47]

We can define frailty reasonably well, but can we intervene in frailty in a meaningful way? Numerous interventions have been studied, including exercise, nutrition, nutritional supplementation, occupational therapy, hormonal supplementation, and various cognitive tools. In one of the largest studies (n = 1637), de Souto Barreto *et al*.[48] randomized patients to multidomain interventions consisting of cognitive training (memory and reasoning), nutrition counseling, and advice on physical activity. These authors performed the multidomain interventions in the form of 12 2-h sessions during the first 2 months, followed by a 1-h session each month until the end of the study. In patients randomized to multidomain intervention, they demonstrated decreased risks of developing both frailty (hazard ratio 0.72; 95% CI 0.55–0.93) and persistent frailty (hazard ratio 0.53; 95% CI 0.33–0.85) compared with controls. Apóstolo *et al*.[49] conducted a systematic review of different interventions to prevent pre-frailty and frailty progression, and they were able to identify multiple effective options.[13] Group exercise programs were shown to be effective in preventing frailty progression, and favorable effects on frailty indicators were demonstrated for physical exercise with supplementation, supplementation alone, cognitive training, and combined treatments. Interestingly, individual exercise programs, hormonal supplementation, and problem-solving therapies were not shown to be effective.

As populations around the globe age, the pre-operative assessment of frailty will become progressively more essential to pre-operative risk stratification and planning. It is incumbent on clinicians to consider the frailty of each individual patient when offering a surgical intervention and consider interventions that may delay frailty progression.

Malnutrition

Undernutrition is more common in the elderly population and has been consistently associated with worse outcomes—including physical function, healthcare utilization, and longer lengths of stay.[50,51] Some data suggest that around a quarter of elderly patients are either malnourished or at nutritional risk.[52] Unfortunately, there is no gold standard for the diagnosis of malnutrition. Malnutrition encompasses both starvation and inflammation-induced catabolic effects such as insulin resistance, wasting, and immune suppression. A post hoc analysis of data from a large prospective randomized trial (EFFORT) demonstrated that systemic inflammation is a negative determinant for response to nourishment (i.e., the higher the C-reactive protein, the less likely nourishment is to benefit the patient).[53] Computerized tomography scan and ultrasound lean body mass are gaining popularity in the evaluation of sarcopenia as a risk factor for perioperative complications.[54] Further complicating the picture is the frequently concomitant, vaguely defined pathologies like sarcopenia, cachexia, and frailty.[55] Sarcopenia can be broadly defined as a syndrome of loss of muscle mass, strength, and performance, while cachexia is a loss of body weight and muscle mass and weakness that occurs in the context of an underlying disease. Unlike cachexia, sarcopenia does not require the presence of an underlying illness. Frailty is a complex pathology that will be discussed in detail later in this article, but both sarcopenia and cachexia can be frequent components of its diagnosis.

Nutrition strategies in critically ill patients

In critically ill patients, a caloric goal of 12 to 25 kcal/kg/day in the first 7 to 10 days is recommended.[19] A common practice is to start with "trophic feeding" (10–30 mL/h) and then incrementally increase it over a few days to the caloric goal. This approach has been demonstrated to be effective by the EDEN trial, which was a multi-center study comparing full enteral nutrition to low-volume enteral feeding (i.e., full versus trophic feeding) for six days, on 1000 mechanically ventilated patients with acute lung injury. In this study, no differences in the number of ventilator-free days, 60-day mortality, frequency of infectious complications, or long-term physical or neurocognitive function were found. However, the low-volume feeding group had less vomiting, smaller gastric residual volumes, lower mean plasma glucose levels, less insulin and prokinetic requirement, and less constipation.[56] An alternative, aggressive feeding, or intensive medical nutrition therapy (IMNT; provision of >75%) may potentially be harmful to patients. In a RCT of 3957 ICU patients, energy-dense formula providing 600 kcal extra nutrition did not make any difference in ventilator-free days, duration of hospital stay, or infection rate.[57] In patients at high risk of aspiration, a post-pyloric feeding tube is preferred[58] Interventions such as using prokinetic (metoclopramide) pre-insertion or a weighted tube have been used to help placing a post-pyloric feeding tube.[59] Between the American Society for Parenteral and Enteral Nutrition (ASPEN) 2016 and ASPEN 2021 guidelines, two large multi-center RCTs were completed and published. These studies were both comparing parenteral nutrition (PN) to enteral nutrition (EN) within 36 h of admission[60] or 24 h after intubation.[57] There was a significant reduction in pneumonia (OR 0.27, 95% CI 0.10–0.70) when early enteral was compared with late enteral feeding, while there was a non-significant trend toward a reduction in pneumonia when early enteral was compared with parenteral nutrition (OR 0.80, 95% CI 0.63–1.00).[61] However, subsequent meta-analyses have failed to show any difference in outcomes between enteral and parenteral nutrition when patients able to receive enteral were randomized to enteral or parenteral nutrition.[62] Based upon existing evidence, there does not appear to be a significant difference in outcomes between PN and EN. The key points of ASPEN and ESPEN recommendations are given in Table 1.

Nutritional components

Dextrose

The caloric contribution of dextrose in parenteral solutions is 3.4 kcal/gm. This is different from dietary carbohydrate which is 4 kcal/gm. The water used to prepare parenteral solutions is the reason behind this difference. There are different concentrations of dextrose solutions available, most commonly 40, 50, and 70%.

Protein

Some observational studies have demonstrated high-protein enteral nutrition to be associated with improved mortality.[63] One prospective observational cohort study of 886 mechanically ventilated patients reported a 50% reduction in 28-day mortality in patients who reached their protein target (hazard ratio 0.47, 95% CI 0.31–0.73).[64] Notably, this study was confounded by the fact that patients who reached their protein target were less sick than the comparison group that reached only their energy needs. Larger prospective RCTs are needed to definitively answer this question. Due to the paucity of trials with high-quality evidence, it is recommended to follow the ASPEN 2016 and 2021 guidelines that suggest 1.2–2.0 g/kg/day.

Fat

The caloric contribution of a typical lipid emulsion is 10 kcal/g or 2 kcal/mL in 20% emulsion and 11 kcal/g or 1.1 kcal/mL in 10% emulsion.

Oral nutritional supplements

Advantages to oral nutritional supplementation compared with usual care have been reported in both trials and systematic reviews and include gains in body weight, dietary intake improvements, and reductions in complications (e.g., infectious complications and post-operative complications).[65]

Multivitamins and trace elements

For critically ill patients receiving parenteral nutrition, the inclusion of multivitamins and trace elements has been suggested that is beyond this review to assess them one by one.

In conclusion, anesthesiologists and intensivists need to be better educated about specific issues related to the geriatric population and attain more competencies.[66] We should be more involved in the discussion on the utility of surgery and have an informed consent discussion with the elderly patients particularly the frail ones or those at risk. Better-designed RCTs could clarify the best nutrition strategy postop and the benefit of regional vs GA. We will also need evidence-based protocols to preserve cognition perioperatively. We hope that our colleagues will use this information to improve their daily practice in managing older patients.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Key points of ASPEN and ESPEN recommendations

	Most recent recommendations	Changes from previous guidelines
Start	Medical nutrition therapy for all ICU patients for more than 48 h	The cutoff was better defined
Route	Oral diet preferred over EN or PN in critically ill patients who are able to eat	No change
Dose	12 to 25 kcal/kg in the first 7–10 days of ICU stay	This differs from 2016 ASPEN guideline favoring early EN strategies based on nutrition assessment and patient condition
Protein	Protein intake of 1.2–2.0 g/kg/day	No change
Shock	In shock patients, low dose EN as soon as shock is controlled	No change
PN/EN	PN or EN in the first week of critical illness	the 2016 ASPEN-SCCM guideline suggested to withhold PN for 7 days in patients with low nutrition risk who are unable to tolerate EN but to use PN in patients at high nutrition risk or those with malnutrition
SPN	No need for SPN prior to day 7 of ICU admission	More RCTs are needed to clarify initiation timing and dosing of SPN in critically ill patients

ASPEN: American Society for Parenteral and Enteral Nutrition, PN: Parenteral nutrition, EN: enteral nutrition, SPN: Supplemental parental nutrition

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