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Editor's Note

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Inflammation occurs in acute and chronic disease states and can influence or be influenced by nutrition. This issue of *Nutrition in Clinical Practice* includes several articles that highlight the relationships between inflammatory conditions and nutrition. The first article in this issue, by Taeb, Hooper, and Marik, provides an overview of sepsis—defined as a dysregulated inflammatory response to infection. The article describes sepsis and systemic inflammatory response criteria, as well as the pathophysiology of sepsis. The authors then review the management of sepsis, including use of antimicrobials, fluid, vasopressors, and corticosteroids. Understanding these concepts is important to allow clinicians to determine which nutrition support therapies will best support critically ill patients. The next paper, by Lheureux and Preiser, tackles the issue of providing nutrition support to patients with acute inflammation–related critical illness. The authors describe the postinjury metabolic response as well as hypermetabolic and recovery phases of critical illness. The article also analyzes the neurologic, endocrine, inflammatory, and immune responses to metabolic stress. The authors then expound on the nutrition sequelae related to metabolic stress, such as changes in energy expenditure and nutrient metabolism.

The article by Drs Ricker and Haas examines chronic inflammation and nutrition, focusing on consumption of anti-inflammatory foods. This review evaluates types of carbohydrates and fats that induce inflammation, as well as components of foods that are anti-inflammatory, such as polyphenols. It also analyzes various dietary patterns as a way to reduce inflammation, including the role of tea, alcohol, spices, and herbs in an anti-inflammatory diet plan.

The type and quantity of macronutrients influence inflammation, but micronutrients also have a role. Vitamin D is a micronutrient with immunomodulatory properties, and it is the focus of an article by Limketkai and colleagues exploring vitamin D and inflammatory bowel disease. The authors first explain the role that vitamin D has within the immune system. They also explain the bidirectional interaction between vitamin D and inflammatory bowel disease (IBD): how vitamin D status may have a causal relationship with IBD and, conversely, how IBD may influence vitamin D status. The final section addresses vitamin D supplementation.

In addition to articles on inflammation, this issue includes those addressing a range of nutrition support topics. Browse the rest of the issue to learn more about parenteral and enteral nutrition in pediatric and adult patients and across inpatient and outpatient settings.

Jeanette M. Hasse, PhD, RD, LD, FADA, CNSC
Editor-in-Chief, *NCP*

Invited Review

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Sepsis: Current Definition, Pathophysiology, Diagnosis, and Management

Abdalsamih M. Taeb, MD[1]; Michael H. Hooper, MD, MSc[1]; and Paul E. Marik, MD, FCCM, FCCP[1]

Abstract

Sepsis is a clinical syndrome that results from the dysregulated inflammatory response to infection that leads to organ dysfunction. The resulting losses to society in terms of financial burden, morbidity, and mortality are enormous. We provide a review of sepsis, its underlying pathophysiology, and guidance for diagnosis and management of this common disease. Current established treatments include appropriate antimicrobial agents to target the underlying infection, optimization of intravascular volume to improve stroke volume, vasopressors to counteract vasoplegic shock, and high-quality supportive care. Appropriate implementation of established treatments combined with novel therapeutic approaches promises to continue to decrease the impact of this disease. (*Nutr Clin Pract*. 2017;32:296-308)

Keywords

sepsis; nutritional support; systemic inflammatory response syndrome; intensive care unit; critically ill

Sepsis is a clinical syndrome that results from the dysregulated inflammatory response to infection that leads to organ dysfunction.[1–3] Sepsis is associated with high morbidity and mortality,[4,5] with estimates of more than $20 billion in annual U.S. healthcare expenditures.[6] The incidence of severe sepsis in the United States is estimated to be about 300 cases per 100,000 population.[2,4,7] Sepsis is among the most common reasons for admission to intensive care units (ICUs) throughout the world.[8] An epidemiologic study in European ICUs demonstrated an incidence of 37% for sepsis and 30% for severe sepsis.[9] Even with optimal treatment, mortality is estimated to be ≥10% from sepsis and ≥40% from septic shock.[1]

The in-hospital mortality of sepsis and septic shock has been declining in the United States from 36% to 26% in a data analysis from 2004–2009.[7] In the absence of widespread use of therapies directly targeting the disease, this mortality improvement is likely related to improvements in the timeliness of antibiotics and resuscitation, as well as improvements in the general delivery of critical care, including improving clinical nutrition. Our review provides an understanding of the definition of sepsis, its underlying pathophysiology, and guidance for diagnosis and management. Understanding the pathophysiology of sepsis will assist any clinician involved in the multidisciplinary care of these critically ill patients.

Definition

A 1991 consensus conference[10] established criteria for the host systemic inflammatory response syndrome (SIRS). Sepsis was defined as infection leading to the onset of SIRS (Table 1). Sepsis complicated by organ dysfunction was termed *severe sepsis*, which could progress to septic shock, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation." A 2001 task force[11] recognized limitations with these definitions and expanded the list of diagnostic criteria, but it did not offer alternatives due to a lack of supporting evidence. In effect, the definitions of sepsis and septic shock have remained unchanged for more than 2 decades.

A 2016 task force generated by national societies, including the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), proposed a new definition of sepsis, termed *Sepsis-3*. The new proposition defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,12,13] As part of their evaluation of criteria for identifying septic patients, they compared traditional SIRS criteria with other methods, including Logistic Organ Dysfunction System (LODS) and Sequential Organ Failure Assessment (SOFA) scoring. Based on this analysis, the authors recommended use of SOFA scoring to define the organ dysfunction of a potentially septic patient (Table 2). Compared with SIRS criteria in

From [1]Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, Virginia, USA.

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Corresponding Author:
Paul Marik, MD, FCCM, FCCP, Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Internal Medicine, Suite 410, 825 Fairfax Av, Norfolk, VA 23507, USA.
Email: marikpe@evms.edu

Table 1. Systemic Inflammatory Response Syndrome (SIRS) Criteria.

SIRS Criteria (Any 2 of the Following)	Value
Heart rate, beats/min	>90
Respiratory rate, beats/min	>20
Temperature, °C	>38 or <36
White blood cell count	>12,000/mm^3 or <4000/mm^3 or >10% bandemia

the University of Pittsburgh and Kaiser Permanente databases, inclusion of SOFA scoring to define sepsis resulted in significantly improved predictive value in terms of mortality. Among critically ill patients with suspected sepsis, the predictive validity of the SOFA score for in-hospital mortality was superior to that for the SIRS criteria (area under the receiver operating characteristic curve [AUCROC] 0.74 vs 0.64). Patients who fulfill these criteria have a predicted mortality of ≥10%. Although the predictive capacity of SOFA and LODS was similar, SOFA is considered easier to calculate and was therefore recommended by the task force. Other studies have supported the idea that SIRS is not an ideal marker for sepsis. Kaukonen et al[14] evaluated the presence of the SIRS criteria in 109,603 patients with infection and organ failure. In this study, 12% of patients were classified as having SIRS-negative sepsis (ie, had <2 SIRS criteria). Furthermore, SIRS criteria are present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes.[15,16]

Septic shock is a type of vasoplegic, distributive shock that occurs following the onset of infection. The 2001 task force definitions described septic shock as "a state of acute circulatory failure."[11] The 2016 SCCM/EISCM task force discussed above favored a broader view to differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities. Septic shock was defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.[1,12,13] The clinical criteria to identify those patients described septic patients who, despite adequate fluid resuscitation, require vasopressors to maintain a mean arterial pressure (MAP) ≥65 mm Hg (circulatory dysfunction) and have a lactate >2 mmol/L (>18 mg/dL) (cellular dysfunction).

The overall effect of the 2016 SCCM/EISCM task force recommendations is to eliminate the concept of sepsis without organ dysfunction, to redefine the clinical criteria for identifying a septic patient, and to redefine the clinical criteria for septic shock. Although the introduction of the Sepsis-3 definition is relatively new to the critical care literature, it is likely to be adopted as a consensus definition for future clinical research. Use of SOFA scoring in clinical trials is already commonly performed and a routine part of data collection for clinical trials in the ICU. Due to the complexity of SOFA scoring, lack of data in many patients, and the concern that it may identify patients later than other methods, the use of the Sepsis-3 method in clinical practice may not prove practical. Recognizing that SOFA scoring had practical limitation, the 2016 SCCM/ESICM task force described an easier method, termed *quick SOFA* (qSOFA), to facilitate the identification of patients potentially at risk of dying of sepsis.[1,12,13] This score is a modified version of the SOFA score. The qSOFA only has 3 components that are each allocated 1 point (Table 3). A qSOFA score ≥2 points indicates organ dysfunction.

Outside of the ICU, qSOFA showed a positive correlation with SOFA scoring (α = 0.73; 95% confidence interval [CI], 0.73–0.74), LODS (α = 0.79; 95% CI, 0.78–0.79), and SIRS (α = 0.69; 95% CI, 0.68–0.69). Criticism of these new methods does exist, and some data have begun to emerge illustrating the limitations of the new definitions, particularly for early detection of sepsis. A prospective database study in a tertiary Australian medical center aimed to determine the prognostic impact of SIRS and compare the diagnostic accuracy of SIRS and qSOFA.[17] In this study of 8871 emergency room patients (4176 [47.1%] with SIRS), SIRS was associated with increased risk of organ dysfunction (relative risk [RR], 3.5) and mortality in patients without organ dysfunction (odds ratio [OR], 3.2). SIRS and qSOFA showed similar discrimination for organ dysfunction (AUCROC, 0.72 vs 0.73). qSOFA was specific but poorly sensitive for organ dysfunction (96.1%, 29.7% respectively). Although qSOFA ≥2 showed high specificity, poor sensitivity seems to exclude its use as a screening tool.

Pathophysiology

The normal host response to infection is a complex process that localizes and controls bacterial invasion while initiating the repair of injured tissue. It involves the activation of circulating and fixed phagocytic cells, as well as the generation of proinflammatory and anti-inflammatory mediators. The host response to an infection is initiated when innate immune cells, particularly macrophages, recognize and bind to microbial components. This may occur by several pathways. Pattern recognition receptors (PRRs) on the surface of host immune cells may recognize and bind to the pathogen-associated molecular patterns (PAMPs) of microorganisms.[18] PRRs can also recognize endogenous danger signals, so-called alarmins or danger-associated molecular patterns (DAMPs), that are released during the inflammatory insult.[18] The triggering receptor expressed on myeloid cells (TREM-1) and the myeloid DAP12-associating lectin (MDL-1) receptors on host immune cells may recognize and bind to microbial components.[19]

Binding of immune cell surface receptors to microbial components initiates a series of steps that result in the phagocytosis of invading bacteria, bacterial killing, and phagocytosis of debris from injured tissue. These processes lead to activation of a large set of genes with subsequent protein synthesis and signaling.[20] Downstream signaling molecules release proinflammatory cytokines by macrophages involved in the host inflammatory response (eg, tumor necrosis factor–α [TNF-α], interleukin [IL] 1), chemokines (eg, intercellular adhesion

Table 2. Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) Score.[a]

	SOFA Score				
Organ System	0	1	2	3	4
Respiratory PO_2/FiO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation platelets, $\times 10^3/mm^3$	≥150	<150	<100	<50	<20
Liver, bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system, Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal creatinine, mL/d	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output, mL/d				<500	<200

FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PO_2, partial pressure of oxygen.
[a]Adapted from Vincent et al.[155]
[b]Catecholamine doses are given as μg/kg/min for at least 1 hour.

Table 3. Quick Sequential Organ Failure Assessment Criteria.

Criteria	Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mm Hg	1

molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1]), and nitric oxide. This leads to the recruitment of additional inflammatory cells, such as leukocytes. A complete discussion of all involved signaling pathways is out of the scope of this review, but the overall response is highly regulated by a mixture of proinflammatory and anti-inflammatory mediators.[21–23] If the proinflammatory and anti-inflammatory mediators balance each other and the initial infectious insult is overcome, homeostasis will be restored.[24,25] The end result will be tissue repair and healing. Sepsis occurs when the release of proinflammatory mediators in response to an infection exceeds the boundaries of the local environment, leading to a more generalized response. This is believed to result from the uncontrolled production of proinflammatory mediators, the so-called cytokine storm.[26,27]

Sir William Osler was the among the first to recognize that "except on few occasions, the patient appears to die from the body's response to infection rather than from the infection."[28] In general, following a variable time course, patients transition from a predominantly proinflammatory to an anti-inflammatory immunosuppressive state.[25,29–31] Among elderly patients, particularly those with significant comorbidities, the anti-inflammatory response may predominate.[29] Similarly, surgical and trauma patients who become infected appear to transition rapidly to a predominantly anti-inflammatory response.[32] Widespread cellular injury may occur when the immune response becomes generalized, and this is believed to be the precursor to organ dysfunction. The precise mechanism of cellular injury is not fully understood but appears to include mechanisms of tissue ischemia (oxygen deficit),[33–36] cytopathic injury (direct cell injury by proinflammatory mediators and/or other products of inflammation),[37,38] and an altered rate of apoptosis (programmed cell death).[39,40] This results in diffuse endothelial injury, microvascular thrombosis, gaps between the endothelial cells (paracellular leak), and shedding of the endothelial-glycocalyx.[41,42] The combination of these mechanisms contributes to a reduction of functional capillary density, heterogeneous abnormalities in microcirculatory blood flow, and increased capillary permeability.[42,43] The cellular injury described above, accompanied by the release of proinflammatory and anti-inflammatory mediators, often progresses to organ dysfunction. No organ system is protected from the consequences of sepsis.

Recognizing Sepsis

Diagnosis of sepsis relies on assessing a variety of nonspecific signs, symptoms, examination findings, and laboratory values. Advanced age,[44] immunodeficiency, chronic disease (eg, diabetes mellitus, renal failure, hepatic failure), and recent acute illness[45] all measurably increase the risk of sepsis.[46] As discussed previously, SIRS criteria (heart rate, respiratory rate, white blood cell [WBC] count, and temperature) have been stressed due to their inclusion in prior consensus definitions of sepsis. However, the list of signs and symptoms to be considered in clinical practice is much more robust (Table 4). The clinical diagnosis of sepsis is not defined by a widely accepted diagnostic algorithm. The ability to access a diverse set of clinical data, a bedside presence, and abundant experience with septic patients are necessary to ensure that sepsis is reliably identified. Due to the lack of specificity of some variables and the variable time course during which some clinical criteria appear, the diagnosis of sepsis is often more apparent in retrospect than during the prospective reality of clinical care.

Table 4. Clinical Variable Relevant in Establishing a Diagnosis of Sepsis.

Clinical Variable	Marker
Markers of infection	Temperature: Fever or hypothermia
	WBC: Leukocytosis or leukopenia or bandemia
	Elevated CRP
	Elevated procalcitonin
	Examination suggestive of infection
	Radiographic results suggestive of infection
	Known infections or positive microbiologic results
Markers of significant physiologic stress or organ dysfunction	Tachycardia
	Tachypnea or respiratory alkalosis
	Hypotension: Low mean or systolic arterial pressure
	Acute lung injury: Arterial hypoxemia
	Hyperglycemia or hypoglycemia
	Change in mental status
	Coagulopathy: Elevated PT or PTT or low platelets
	Ileus
	Hepatic dysfunction: Hyperbilirubinemia, transaminitis
	Metabolic acidosis
	Hyperlactatemia
	Decreased capillary refill or mottling

CRP, C-reactive protein; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

Absolute confirmation of the diagnosis is not expected in the early phase of the disease. Blood cultures remain an important part of the diagnostic strategy in sepsis. The timing of blood culture collection does not appear to significantly affect the recovery of clinically relevant microorganisms, and most authorities therefore recommend collecting multiple sets simultaneously or over a short period of time.[47] Optimally, 2–3 sets of blood specimens should be collected from independent venipuncture sites, and each set should consist of at least 20 mL of blood.[47] A pathogen is not isolated in between 25% and 50% of patients.[48] Molecular diagnostic techniques aim to improve both the time and the accuracy of our diagnostic testing but remain in their infancy.

A review of the critical care literature reveals hundreds of studies of biomarkers as adjunctive methods to improve the diagnosis of sepsis. Despite monumental efforts, clinical guidelines continue to recommend consideration of a broad range of symptoms, signs, laboratory, and examination findings. No single biomarker receives a strong recommendation for inclusion in the diagnostic criteria for sepsis. The "classic" proinflammatory mediators (IL-1, IL-6, and TNF-α) are unable to distinguish between infectious and noninfectious causes of SIRS. Procalcitonin (PCT), a propeptide of calcitonin normally produced in the C cells of the thyroid, increases in septic patients. A recent meta-analysis showed a sensitivity of 77% and specificity of 79%.[49] This diagnostic accuracy is better than any other single test to diagnose sepsis. A PCT >0.5 ng/mL is suggestive of a bacterial infection while a level <0.1 ng/mL makes bacterial infection much less likely.[50] The optimal diagnostic threshold is unclear and has been reported to vary from 0.25–1.4 ng/mL.[49] This variation of diagnostic threshold may partly be explained by the case mix of each study and the fact that patients with gram-negative infection have significantly higher PCT levels than those with gram-positive infections.[51,52] In addition to being a very useful test to diagnose bacterial sepsis, the trend in the PCT level is useful for deciding when to discontinue antibiotics.[53]

Management of Sepsis

The optimal management of patients with severe sepsis and septic shock remains controversial, although certain fundamental goals are shared among most clinicians and authors. Rapid administration of antibiotics, early identification of the source of infection (with source control if feasible), prompt resuscitation, and multidisciplinary care teams are widely accepted as appropriate care. It is important to emphasize, however, that there is no level 1 evidence for single intervention that reduces mortality in patients with sepsis or septic shock. We will detail the various facets of sepsis care and highlight the controversies within those aspects of care.

Antimicrobial Therapy

Prompt and effective treatment of the active infection is essential to the successful treatment of sepsis and septic shock. Empiric intravenous (IV) antibiotic therapy should be started as soon as possible after appropriate cultures have been obtained.[54] While the tight window as suggested by current guidelines (administration within 3 hours of emergency department triage and within 1 hour of severe sepsis/septic shock recognition) is not supported by high-grade scientific evidence like randomized controlled trials (RCTs) or meta-analysis,[55] common sense would dictate that delaying the administration of antibiotics serves no useful purpose. Observational data are compelling in their support of early antibiotics. Kumar et al[56] published an often-cited study of 2731 patients with septic shock and demonstrated that the time to initiation of appropriate antimicrobial therapy was the strongest predictor of mortality. The choice of antibiotics can be complex but important. A number of studies have demonstrated that appropriate initial antimicrobial therapy, defined as the use of at least 1 antibiotic active in vitro against the causative bacteria, is associated with a lower mortality compared with patients receiving initial inappropriate therapy.[57,58] The goal is to estimate the probability that a specific organism is the cause of a patient's sepsis and then appropriately weigh the risk and benefit of empiric treatment based on the estimated probability and possible side effects of the antimicrobial agent. Suspicion of causative organisms is informed by the patient's history (eg, recent antibiotics received[59]), comorbidities, clinical context (eg, community or hospital acquired), Gram stain data, and local

resistance patterns and whether the patient has risk factors for a drug-resistant pathogen (eg, recent hospitalization, recent antibiotics, nonambulatory status, tube feeding, immunocompromised status, acid-suppressive therapy, chronic hemodialysis, or history of methicillin-resistant *Staphylococcus aureus*).[60–62] Prior to definitive identification of a pathogen, empiric combination therapy is commonly practiced in the United States, and there are little data to refute that practice.

Studies do not support the routine use of prophylactic antifungals in the nonneutropenic, critically ill patient.[63] The empiric treatment of invasive fungal disease in critically ill patients remains a topic of debate. The 2016 Infectious Diseases Society of America (IDSA) guidelines[64] recommend empiric antifungal coverage in some cases. Individual trials have not consistently supported this recommendation in subsets of the population described. A trial in adults with ICU-acquired sepsis and *Candida* colonization in multiple sites did not show that treatment with micafungin was associated with improved survival.[65] A similar study using fluconazole showed a similar lack of efficacy.[66] These trials do not refute the use of empiric antifungal treatments in all critically ill patients but do support the need to further refine our methods for identifying patients who will benefit from treatment.

Once a pathogen is isolated, "antimicrobial de-escalation[67]" is associated with lower rates of hospital mortality and widely recommended. The average length of antibiotic treatment varies between and within different countries and healthcare settings, independent of factors such as disease severity.[68] Interventional trials to shorten antibiotic duration have often shown no difference in shorter (5–7 days) vs longer (10–14 days) of antibiotic therapy.[69–71]

The physical measures undertaken to eradicate a focus of infection and eliminate or treat ongoing microbial proliferation and infection are collectively termed *source control*. Source control should be pursued in septic patients since unaddressed foci of infection may lead to uncured infection and death.[8,54] Just as there is no RCT data to support the use of antibiotics in sepsis, RCTs of source control vs a lack of source control do not exist. Observational data support that increased time to definitive source control is associated with increased mortality in certain types of infections.[72,73]

Fluid Therapy

The appropriate administration of fluids to patients with severe sepsis is an important topic of debate in critical care. More intensive treatment may cause iatrogenic injury.[74] Volume resuscitation is likely not an exception. Traditional teaching is that aggressive fluid resuscitation is the best initial approach for hypotension in sepsis. However, no human data show that large fluid boluses (>30 mL/kg) reliably improve blood pressure, urine output, or end-organ perfusion.[75] This approach may lead to respiratory failure (ie, "iatrogenic salt water drowning") and kidney injury.[76] The physiologic rationale for administering a fluid bolus is to increase stroke volume (SV). If SV does not increase, then the fluid bolus has no useful purpose and may be harmful. This concept is referred to as "fluid responsiveness."[77,78] By definition, a patient is considered to be fluid responsive if his or her SV increases by ≥10% following a fluid challenge (usually a passive leg raise or a 500-cc crystalloid bolus). The chest radiograph, central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), and routine ultrasonography, including the vena-caval collapsibility index, have limited value in gauging fluid responsiveness and should be used with caution.[79–82] The passive leg-raising (PLR) maneuver and a fluid challenge coupled with real-time SV monitoring are accurate methods for determining fluid responsiveness.[77,83,84]

Multiple studies of diverse populations show that about 50% of hemodynamically unstable patients are fluid responsive.[77,78] This implies that for about 50% of hemodynamically unstable patients, fluid boluses may be harmful.[76] This challenges the concept that fluid boluses are a low-risk cornerstone of resuscitation. Large fluid boluses may decrease diastolic compliance of the ventricles, causing the CVP to increase more than the mean circulating filling pressure (MCFP), paradoxically decreasing the gradient for venous return.[85] The increased CVP may lead to increasing venous pressure and impair organ function and microcirculatory flow, particularly for encapsulated organs such as the kidney and liver.[76] To make matters worse, the hemodynamic response to fluids in patients with circulatory shock is brief as >90% of the fluid leaks into the tissues.[86,87] In a systematic review of the hemodynamic response of fluid boluses in patients with sepsis,[88] the MAP increased by 7.8 ± 3.8 mm Hg immediately following the fluid bolus, but within an hour, the MAP had returned to baseline with no increase in urine output. Fluid boluses may cause a fall in effective arterial elastance and systemic vascular resistance, potentiating arterial vasodilatation and the hyperdynamic state.[89,90]

The harmful effects of overaggressive fluid resuscitation on the outcome of sepsis are supported by experimental models,[91] as well as data accumulated from clinical trials. Multiple clinical studies have demonstrated an independent association between a positive fluid balance and increased mortality in patients with sepsis.[3,92–98] In a secondary analysis of the Vasopressin in Septic Shock Trial (VASST), Boyd and colleagues[98] demonstrated that a greater positive fluid balance at both 12 hours and 4 days was an independent predictor of death. An observational study of septic patients at the Mayo clinic showed that 67% of patients had clinical evidence of fluid overload at 24 hours, with 48% having evidence of fluid overload at 72 hours. Fluid overload was an independent predictor of mortality (OR, 1.92; 95% CI, 1.16–3.22).[99] Overly aggressive fluid resuscitation can result in intra-abdominal hypertension, which is associated with a high risk of complications and death.[100] In children and atypical patient populations (compared with U.S. hospitals), the most compelling data that fluid loading for sepsis is harmful come from the landmark

Fluid Expansion as Supportive Therapy (FEAST) study performed in 3141 sub-Saharan children with severe sepsis.[101] In this RCT, aggressive fluid loading was associated with a significantly increased risk of death.

These data support a "conservative," hemodynamically guided fluid resuscitation strategy in patients with severe sepsis and septic shock. This is in agreement with recent trends in critical care literature that have supported a "less is more" approach in which the aims are largely to employ interventions that will maintain or restore normal physiology. Over the course of human evolution, it is reasonable to assume that hypovolemia has exerted selective pressures and resulted in compensatory mechanism. The same cannot be said for hypervolemia. Current guidelines still support an initial large-volume fluid resuscitation of 30 cc/kg, followed by subsequent fluid management strategies that often lead to hypervolemia. As detailed above, emerging literature contradicts this historical standard. No RCTs have selectively tested the use of a liberal fluid strategy in the initial resuscitation of septic patients. We anticipate that the standard of care will shift toward a conservative strategy as additional studies emerge.

The choice of fluid in patients with severe sepsis and septic shock is also controversial. Balanced salt solutions (lactated Ringers solution, Hartmann's solution, Plasma-Lyte 148 [PL-148]) are available and advocated by many authors. Normal saline (0.9% NaCl) is the most widely used crystalloid around the world. However, normal saline is an unphysiological solution that is associated with a number of adverse effects. Normal saline causes a hyperchloremic metabolic acidosis,[102–104] decreases renal blood flow,[105] and increases the risk of renal failure.[106] In patients with sepsis, the use of normal saline compared with physiological salt solutions has been associated with an increased risk of death.[107] The 0.9% Saline vs PL-148 for ICU fluid Therapy (SPLIT)[108] trial was a randomized double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand that compared 0.9% saline with PL-148 for ICU fluid therapy. The risk of acute kidney injury (AKI) (primary outcome) as well as all secondary outcomes did not differ between the 2 fluid groups. This study has a number of significant limitations that may preclude the generalizability of the results; most notably, 71% of patients were postoperative patients, only 4% were diagnosed with sepsis, and the volume of fluid administered was small (about 2.7 L in the first 4 days). While the SPLIT trial may help inform that the outcome difference between patients who receive normal saline or balanced solutions is unlikely to be dramatic, the scientific rationale and supporting data for administering balanced solutions are superior.

Synthetic starch solutions increase the risk of renal failure and death in patients with sepsis and should be avoided.[109] The role of serum albumin for patients with sepsis is assessed in multiple clinical trials and remains a subject of debate.[110] Nevertheless, the use of 4% serum albumin in patients with sepsis was not associated with a survival benefit in the Saline versus Albumin Fluid Evaluation (SAFE) study.[111] In the Albumin Italian Outcome Sepsis (ALBIOS) study, serum albumin (20%) was not associated with survival benefit in patients with severe sepsis or septic shock. However, meta-analysis of multiple RCTs showed the 90-day mortality of patients with septic shock decreased significantly in patients resuscitated with serum albumin compared with crystalloid and saline.[112] It should be noted that exogenous serum albumin is one of the few therapies that can restore the endothelial glycocalyx in experimental systems.[113] The use of a continuous infusion of hyperoncotic serum albumin (20% or 25%) in patients with "resuscitated" septic shock may help to stabilize the glycocalyx as seen in these experimental systems, although high-level clinical data supporting this recommendation are still lacking.

Vasopressors and Inotropic Agents

A low MAP is a reliable predictor for the development of organ dysfunction. When the MAP falls below an organ's autoregulatory threshold, organ blood flow decreases in a linear fashion.[114] Since the autoregulatory ranges of the heart, brain, and kidney are >60 mm Hg, a MAP below this level will more likely result in organ ischemia.[115] Mortality in populations with septic shock is associated with mean arterial blood thresholds <65 mm Hg.[116] In the SEPSISPAM study (Assessment of Two Levels of Arterial Pressure on Survival in Patients with Septic Shock),[117] patients with septic shock were randomized to achieve a target MAP of 65–70 or 80–85 mm Hg with a primary outcome of 28-day mortality. Overall, there was no difference in either the primary or secondary end point between the 2 treatment groups. However, the incidence of organ failure (particularly renal dysfunction) was higher in the subgroup of patients with chronic hypertension in the lower MAP group. Furthermore, the time below the 65-mm Hg (but not 80-mm Hg) threshold was an independent predictor of death. Based on these data, we suggest targeting an initial MAP of 65–70 mm Hg for patients with septic shock. Among those patients with a history of chronic hypertension, it may be preferable to target a slightly higher MAP (80–85 mm Hg).

Norepinephrine is the vasopressor of choice for patients with septic shock.[54,118] Dopamine increases the risk of arrhythmias and death and should be avoided in most cases. Similarly, phenylephrine is not recommended as the first-line vasopressor. There is concern of decreases in cardiac output as well as renal and splanchnic blood flow.[119] In patients with septic shock, norepinephrine restores the stressed blood volume, venous return, and cardiac output. Norepinephrine increases arterial vascular tone, further increasing blood pressure and organ blood flow.[8] Venous capacitance vessels are much more sensitive to sympathetic stimulation than are arterial resistance vessels; consequently, low-dose α-1 agonists cause greater venoconstriction than vasoconstriction.[120,121] The increase in the stressed blood volume following the use of norepinephrine is due to the mobilization of blood rather than a short-lived volume expander (crystalloid). Therefore, unlike fluids, the effect of α-1 agonists on venous return is

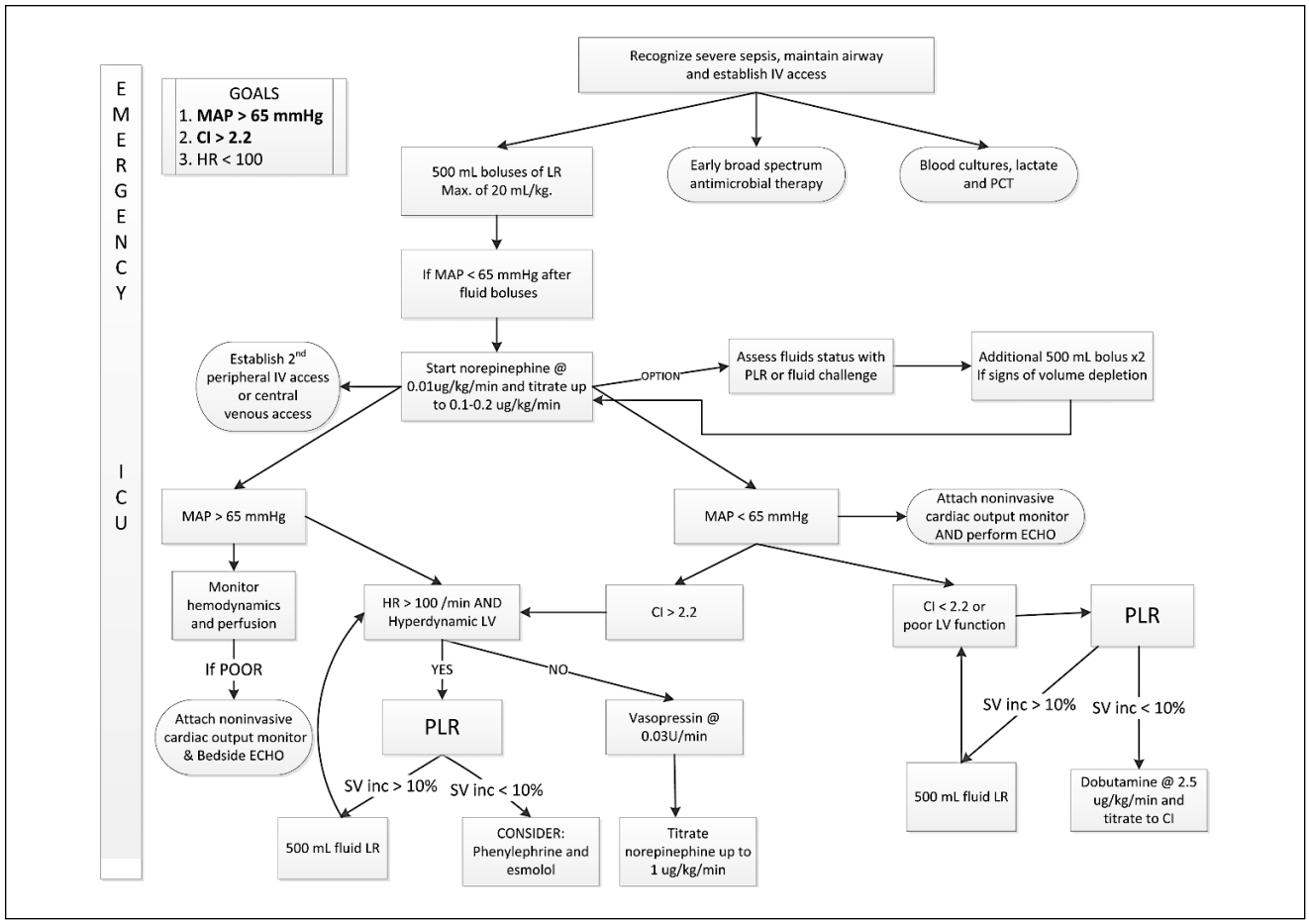

Figure 1. Suggested initial approach to the management of patients with sepsis and septic shock. CI, cardiac index; ECHO, echocardiography; HR, heart rate; ICU, intensive care unit; inc, increase; IV, intravenous; LR, lactated Ringers solution; LV, left ventricle; MAP, mean arterial pressure; Max, maximal; PCT, procalcitonin; PLR, passive leg raising; SV, stroke volume.

enduring and not associated with tissue edema. The early use of norepinephrine in patients with septic shock can increase preload, rendering the fluid-responsive patient fluid unresponsive.[121] This may allow the target blood pressure to be achieved and a significant reduction in the amount of fluid administered. Hamzaoui et al[122] have demonstrated that the early administration of norepinephrine increased preload, cardiac output, and MAP, largely reversing the hemodynamic abnormalities of severe vasodilatory shock. Abid and colleagues[123] demonstrated that the early use of norepinephrine in patients with septic shock was a strong predictor of survival. For patients with persistent hypotension and hyperdynamic ventricular function (who have severe failure of vasomotor tone), fixed-dose vasopressin (0.03 U/min) is a reasonable second agent to be initiated. Vasopressin reverses the "relative vasopressin deficiency" seen among patients with septic shock and increases adrenergic sensitivity.[124] Data on early use of vasopressin (in addition to norepinephrine) did not suggest a significant survival benefit, and therefore it is not strongly recommended unless a second vasopressor is needed.[125] In patients with concomitant left ventricular function, use of an inotropic agent such as dobutamine may be considered.

A potential treatment algorithm for the hemodynamic stabilization of patients with septic shock is provided in Figure 1. It is similar to the Bathurst-USCOM hemodynamic (BUSH) protocol[126] with early pressors and conservative fluids in the first 24 and 48 hours. It is important, however, to emphasize that each patient has unique hemodynamics, comorbidities, and response to treatment.[127] Therefore, these algorithms must be adapted dynamically to each patient based on individual characteristics and variations.

Resuscitation End Points

A large number of hemodynamic, perfusion, oxygenation, and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock.[54,128] Most of these targets, however, are controversial and have not been individually assessed in high-quality outcomes research.

Recently, 3 separate multicenter clinical trials using rigid protocols with fixed resuscitation targets failed to show any evidence of benefit vs resuscitation driven by bedside physicians.[129–131] CVP is commonly measured and endorsed as a resuscitation target.[54] However, as detailed previously, CVP does not correlate with fluid responsiveness, and elevated CVP is associated with poor outcomes. While urine output may be a valuable marker of renal perfusion in hypovolemic states, this clinical sign becomes problematic for sepsis-associated AKI where experimental models suggest that oliguria occurs in the presence of marked global renal hyperemia.[132–134] Titration of fluids to urine output may therefore result in volume overload without benefit to renal function. Lactate is also frequently used as a clinical target, but it remains unclear which interventions should be administered to a patient with an elevated lactate level. The Surviving Sepsis Campaign recommends "targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion."[54] This recommendation is based on the notion that an elevated lactate is a consequence of tissue hypoxia and inadequate oxygen delivery[135] and is supported by 2 studies that used lactate clearance as the target of resuscitation.[136,137] Multiple studies have demonstrated that the increased blood lactate concentration in sepsis is not caused by tissue hypoxia but is rather produced aerobically as part of the metabolic stress response.[138–141] The assumption that sepsis is associated with tissue hypoxia is possibly incorrect.[138,140] Increasing oxygen delivery for patients with sepsis is not necessarily associated with improved outcomes.[142] Previous studies have demonstrated that targeting supramaximal oxygen delivery does not improve outcome and may be harmful.[143,144] A study on β blockade in sepsis showed that oxygen delivery was reduced in the esmolol arm, yet the lactate concentration decreased among esmolol arm subjects, whereas it increased for the control arm patients.[145]

The updated Surviving Sepsis Campaign guidelines, which are now adopted as a mandatory reported metric in the United States (National Quality Forum Measure 0500, Centers for Medicare & Medicaid Services SEP-1 Quality measure), require reassessment of volume status and tissue perfusion (after a 30-mL/kg fluid bolus) with either "repeat focused exam by a licensed independent practitioner including vital signs, cardiopulmonary refill, pulse and skin findings" (all these clinical findings) or 2 of the following: CVP, $ScvO_2$, bedside cardiovascular ultrasound, or dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge. However, as described previously, it has been shown that the CVP, $ScvO_2$, and ultrasonography, including the vena-caval collapsibility index, have very limited value for predicting the response to fluid administration and should not be used for this purpose.[79,80,82] Furthermore, data suggest that physical examination cannot be used to predict fluid responsiveness, and physical examination is unreliable for estimating intravascular volume status.[146]

The poor performance of many proposed quantitative targets for resuscitation suggests that we need a new approach that focuses care on more reliable targets and allows individual variation by thoughtful bedside clinicians. Achieving a MAP of at least 65 mm Hg would be a reasonable primary target for the resuscitation of patients with septic shock. Notably, however, there are clearly exceptions to this target. Furthermore, it is not possible to prescribe an appropriate therapy for a patient with a MAP <65 mm Hg without taking into account numerous patient characteristics and physiologic variables. Measurement of fluid responsiveness is useful when appropriate methods are employed.[83,84] Use of passive leg raising allows a direct comparison of a patient's physiologic status prior to and immediately following an increase in venous return to the right side of the heart. Assessments methods, including echocardiography, bioreactance, and pulse pressure variation, have all been shown to be effective in predicting fluid responsiveness following a passive leg raise maneuver.[83]

Corticosteroids

The use of corticosteroids to treat patients with sepsis has been a part of clinical practice for decades. Literature both supporting its use and refuting its benefit is in abundance. In 2002, interest in corticosteroids to treat sepsis surged after a multicenter, double-blind trial enrolled 300 patients to receive either placebo or hydrocortisone plus fludrocortisone for vasopressor-dependent shock.[147] Hydrocortisone administration decreased 28-day mortality (55% vs 61%) and forwarded the concept of relative adrenal insufficiency. This trial in the context of conflicting evidence from prior trials led to a large multicenter RCT.[148] The Corticosteroid Therapy of Septic Shock (CORTICUS) trial enrolled 499 patients with septic shock (with or without of pressor dependency). They enrolled patients within 72 hours of the onset of shock and randomized patients to either hydrocortisone (50 mg) or placebo intravenously every 6 hours for 5 days, followed by a tapering regimen. Hydrocortisone administration did not improve 28-day mortality (35% vs 32% in the placebo group). Attempts to resolve conflicting data between the French and CORTICUS trials suggest that glucocorticoid therapy may be more likely to benefit patients with severe septic shock who are pressor dependent.[149,150] The observed physiologic benefit (in terms of time to shock reversal) has been consistently demonstrated, but definitive data regarding the effect on patient outcomes in the many subgroups of a heterogeneous septic patient population are not clear.

Currently, the Australian and New Zealand Intensive Care Society Clinical Trials Group is performing the Adjunctive Corticosteroid Treatment in Critically ill patients with septic shock (ADRENAL) study,[151] in which 3800 patients with septic shock will be randomized to receive hydrocortisone (200 mg/d as a continuous infusion) vs placebo. The outcome of this study should assist more scientific decision making when choosing to withhold or administer steroids to a septic patient.

High-Quality Supportive Care

While treatments aimed directly at the infectious cause of sepsis (eg, antibiotics), the dysregulated immune response (eg, steroids), or manipulation of the shock state (eg, vasopressors, fluids) remain the core of sepsis treatment strategies, the use of high-quality supportive care has repeatedly been demonstrated to be associated with improved outcomes in septic patients as well as general critical care populations. A multidisciplinary approach to assessment and management of septic patients is recommended. Nursing, nutrition support, respiratory therapy support, and pharmacy are critical to achieving good outcomes in the ICU. Interventions to minimize sedation, improve mobility, review medications for interactions and appropriateness, avoid nosocomial infections, and reduce barotrauma are among the many iterative decisions that the care team must make on a daily (if not hourly) basis to ensure patient safety and improve outcomes.

Emerging Therapies

The emergence of activated protein C as a targeted therapy for sepsis was celebrated as a significant advance in the care of sepsis. The subsequent evidence of its lack of efficacy,[48] combined with failures of other agents such as lactoferrin,[152] myeloid differentiation factor 2/toll-like receptor 4 (MD2-TLR-4) antagonists,[153] TNF antagonists, and IL-1 antagonists, raised concerns about our ability to affect the pathophysiology of sepsis. Numerous failed trials for the hundreds of agents hypothesized to treat sepsis are available in the review literature. Despite these failures, active investigations into other agents and targets exist. Interventions aimed at healing injured endothelium by targeting tight junctions, antihistones, and novel cytokine antagonists are being pursued. A recently published observational study of a group of consecutive septic patients compared the effects of IV vitamin C, hydrocortisone, and thiamine vs usual care.[154] Extrapolation to clinical care should be cautioned given the retrospective study design, but the significant association with decreased mortality in the intervention group (8.5% vs 40.4%) points to a compelling hypothesis for a future investigation. The low risk and low cost of this intervention, paired with potential for a significant effect on outcomes in a common disease, make the potential impact of this therapy enormous. We hold hope that this or other novel therapies will be discovered and prove effective.

Conclusions

Sepsis is a common disease with a high mortality rate and large financial impact on our healthcare systems. Sepsis arises from dysregulated immune response to infection with organ failure via multiple pathophysiologic mechanisms. Current treatments include appropriate antimicrobial agents to target the underlying infection, optimization of intravascular volume to improve stroke volume, vasopressors to counteract vasoplegic shock, and high-quality supportive care. Many controversies exist regarding the targets and methods for volume resuscitation. Recent trials have supported a flexible approach to resuscitation rather than applying universal methods and target thresholds to all patients. Treatments to manipulate the immune response in sepsis have nearly universally been ineffective in large RCTs. Corticosteroids for the treatment of patients with septic shock remain controversial, and practice variation exists.

In the absence of directed therapies to directly alter the pathophysiology of sepsis, we must focus much of our care on the multidisciplinary support of the septic patient. Poor nutrition support has been directly associated with poor outcomes in patients and is a critical component of optimal care.

Statement of Authorship

A. M. Taeb, M. H. Hooper, and P. E. Marik contributed to conception/design of the manuscript; contributed to acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Invited Review

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Role of Nutrition Support in Inflammatory Conditions

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Olivier Lheureux, MD[1]; and Jean-Charles Preiser, MD, PhD[1]

Abstract

This review intends to summarize recent development on the potential nutrition implications of acute inflammation encountered during critical illness. Different aspects of the inflammatory response and their impact on nutrition management during critical illness will be discussed: the timing of the postinjury metabolic response, the integration of regulatory mechanisms involved in the metabolic response to stress, the oxidative stress, the metabolic and clinical consequences in terms of energy expenditure, use of energy, changes in body composition, and behavior. (*Nutr Clin Pract*. 2017;32:310-317)

Keywords

critical care; nutritional support; critical illness; inflammation; oxidative stress; sepsis

Understanding the pathophysiology of stress has evolved and improved considerably in recent years. The "stress" characterizes the response to any situation that threatens homeostasis. The "metabolic" stress is triggered by an aggression (trauma, surgery, severe infection) and involves a multitude of adaptive mechanisms at the level of the whole organism. The combination of these adaptive mechanisms is intended to protect or maintain the homeostasis in tissues at the cellular and subcellular levels.

Timing of the Postinjury Metabolic Response

The evolution in resting energy expenditure (REE) and other metabolic changes differ during the successive phases. In 1942, Sir Cuthbertson described the evolution of the postoperative phase in 2 phases and compared them with the reflux (ebb phase) and flux (flow phase) of the tide. Typically, during the phase of reflux, nutrients can no longer be effectively used as an energy source. The acute phase corresponds to a systemic inflammatory response, accompanied by massive secretion of inflammatory mediators and "catabolic" hormones, as well as a relative decrease in the secretion of "anabolic" hormones and resistance to anabolic signals.[1] Later, during the flux or late phase, ingested nutrients gradually regain their energy efficiency and may replenish endogenous reserves.

The hypermetabolic phase is characterized by increased flux of metabolic substrates, under the combined effect of stress hormones, fat mediators derived from arachidonic acid, and cytokines.[2]

Today, although this biphasic chronology remains relevant, a third subsequent phase was proposed and seems more suited to the description of the postinjury conditions frequently encountered in intensive care.[3–5] This recovery phase corresponds to the gradual return to normal functioning of different tissues, corresponding to the surgical patient healing phase.

During the hypermetabolic and recovery phases, the need for macronutrients is largely increased to match the rise in REE. The intense stress also causes qualitative metabolic changes. These changes are usually interpreted as adaptive mechanisms to promote metabolic priorities in the whole body.

Integration of Secondary Regulatory Mechanisms With Metabolic Stress

The response to metabolic stress involves a series of neurological adaptive mechanisms, central and autonomous, and also endocrine, inflammatory, and immune pathways at the whole organism. These processes are synergistic.

In chronological order, the central nervous system is the first to be involved via the activation of postganglionic neuron and the adrenal medulla.[6] The activation of the postganglionic neuron causes the release of norepinephrine, which in turn activates the adrenergic receptors.[7] The stimulation of chromaffin

From the [1]Department of Intensive Care, CUB-Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium.

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Corresponding Author:
Jean-Charles Preiser, MD, PhD, Department of Intensive Care, CUB-Erasme, Université Libre de Bruxelles (ULB), 808, Route de Lennik, Brussels 1070, Belgium.
Email: jean-charles.preiser@erasme.ulb.ac.be

cells of the adrenal medulla causes the release of noradrenaline and adrenaline in the bloodstream.[8]

Thereafter, the initiation of a neuroendocrine mechanism occurs in the paraventricular nucleus and induces activation of the hypothalamic-pituitary axis. This causes the release of hormones such as adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), growth hormone (GH), and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary gland. Circulating levels of peripheral hormones released in response to these pituitary factors are reduced, however, except for cortisol.[9]

Inflammatory, immune, and behavioral components are involved later in the metabolic stress response. The inflammatory process is mediated in part by the central nervous system, cytokines, and other mediators.[10–14] Their role is probably important and multifaceted. They affect the metabolic pathways by acting at the level of cellular signaling as well as modifying the regional blood flow and thus influence the transport of energy substrates. The immune component involves both an innate response and a humoral response. It leads to the production of antibodies and cytokines such as tumor necrosis factor–α (TNF-α), interleukin (IL) 1, and IL-6, which promote proteolysis and lipolysis.

Besides these well-characterized pathways, other mediators have been identified recently. These are adipokines (such as leptin, resistin, and adiponectin) secreted by adipose tissue and enterohormones, including ghrelin, cholecystokinin, and peptide YY released by the gastrointestinal (GI) tract. However, the potential roles of these factors in stress response are still largely unknown.

The Development of Inflammatory Response

The prototype of the immuno-inflammatory reaction involves the activation of cells of innate immunity following the detection of a pathogen. This interaction between the immune system and the infectious agent involves the recognition of particular motives expressed by foreign agents and is called a pathogen-associated molecular pattern (PAMP).[15,16] These PAMPs are recognized by specific receptors referred to as pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), the lectin receptors, or intracellular receptors such as nucleotide oligomerization domain (NOD).

However, it is clear that the "immuno-inflammatory" reaction may develop in the absence of any infectious episode, for example, in response to trauma. According to the danger model,[17] the immune system would be sensitive to endogenous signals in the course of tissue injury, whose origin could be infectious or noninfectious (eg, traumatic), and the induced response would be to limit the damage and to restore homeostasis. These signals consist of molecules called damage-associated molecular patterns (DAMPs) or alarmins. They correspond in particular to different intracellular components that can be actively secreted or just released during cell injury. At present, the best-known DAMPs are high-mobility group protein B1 (HMGB1), the S100 proteins, and certain heat shock proteins (HSPs).

Thus, TLR activation will lead to the production of different molecules, including cytokines, chemokines, fat mediators (platelet activating factor, eicosanoids), and derived reactive species of oxygen and nitrogen.[18]

The next step in the immuno-inflammatory reaction allows the extension of the phenomenon by mobilization and activation of immune cells. The mediators produced during the interaction between the pathogen and the immune cells, especially the proinflammatory cytokines IL-1β and TNF-α, will in turn enable a more generalized activation of the immune response by orchestrating a complex network of secondary responses.[15]

Oxidative Stress

In the postinjury period, the increased production of reactive oxygen species (ROS) and the use of antioxidant mechanisms generate a significant oxidative stress. In a major stress, ROS are released in large quantities[19] and contribute to multiorgan failure.[20] To prevent the harmful effects of ROS, the cell uses enzymatic antioxidant systems, such as superoxide dismutase, catalase, and glutathione peroxidase, and nonenzymatic antioxidants, such as vitamin E, vitamin C, and β-carotene. Importantly, trace elements (copper/manganese/zinc, iron, and selenium) are respectively required for superoxide dismutase, catalase, and glutathione peroxidase. The bioavailability of these trace elements is often the rate-limiting factor of the antioxidant enzymes. Suboptimal selenium and zinc serum concentrations worsen oxidative stress.[21] Facing a massive release of free radicals, these defense mechanisms may be overwhelmed or exhausted. Under these conditions, oxidative damage occurs in organelles and in all cellular structures.

In physiological conditions, ROS are necessary for the production of energy within mitochondria, and the cell is protected from the toxic effects of ROS by endogenous antioxidants.[22] The release of ROS is involved in major pathways of cell signaling, allowing the transduction of extracellular stimuli into changes in cell physiology by the modulation of the transcription of some genes or by posttranscriptional modulation. "Redox-responsive" signaling pathways also have been involved in important functions such as the production of nitric oxide, involved in the regulation of vascular tone and neurotransmission, cell adhesion, the immune response, the sensing of hypoxia, and apoptosis.[23,24]

The importance of oxidative stress and the interest in its modulation by antioxidant treatments have been subjects of intense research for years. In the field of nutrition, many consumers and healthcare providers carefully scrutinize the content of antioxidants as a component of regular diets. These supplements are usually extracted from plants and are claimed to contain high amounts of vitamins with antioxidant properties

(mainly vitamins A, C, and E) and trace elements such as selenium, copper, or zinc. Similarly, the beneficial effects of several drugs and medications, thought to be related to their recently discovered antioxidants properties, further support the wave of enthusiasm for the use of antioxidants. However, in contradiction to the belief that oxidative stress is detrimental and should be treated or prevented, several recent studies, meta-analyses, and systematic reviews were unable to confirm the expected benefit of supplemental antioxidants.[25–28] For example, glutamine in the parenteral nutrition (PN) solution is associated with several beneficial effects in terms of immune response, intestinal function, and protein metabolism. More recent studies have not confirmed these benefits; on the contrary, excess mortality was evident in the group of patients supplemented with large doses of glutamine and/or antioxidants.[29,30]

These apparently contradictory findings can only be reconciled by the interpretation of increased oxidative stress as an adaptive mechanism in some instances and as a causal mechanism in pathological conditions. Due to this duality in the roles of oxidative stress, its modulation by antioxidants is a more complex issue than previously thought. In any case, a prolongation of human life span by the intake of antioxidant supplements is not supported. A rigorous scientific evaluation in well-defined conditions is mandatory to define the appropriate place for manipulations of the oxidative pathways in human medicine.[20,31]

Metabolic Consequences

The advances in physiology have allowed a detailed description of the processes involved by the organism in metabolic stress situations, regardless of the initial trigger. The combination of the neurological adaptive mechanisms, central and autonomous, and also endocrine, metabolic, inflammatory, and immune pathway results in increased catabolism and the development of resistance to the anabolic signals, like insulin. This results in a reorganization of delivery of energy substrates by promoting organs whose functioning is essential to the survival of the subject undergoing aggression. The preservation of heart and immune function is predominant with respect to the skin, muscle, and adipose tissue, where an adaptive insulin resistance develops.[32] However, if these metabolic changes persist, they could worsen the damage by increasing muscle wasting, for example.

Clinical Consequences

The clinical consequences of the metabolic stress response are numerous and include a multitude of aspects. Thus, for example, we can mention the circadian variations in metabolism, differences in the use of nutrients as a source of energy, stress hyperglycemia, muscle atrophy, changes in body composition, and behavioral changes. In this section, we aim to describe a broad view of the changes that occur when using macronutrients during stress. Unfortunately, a clear relationship between the dose of nutrients and clinical effects has rarely been reported.

Energy Expenditure of Rest

During the acute phase, the REE is moderately elevated, especially for reasons related to the disease, the administered treatment (fever treatment, sedatives, muscle paralyzers, assisted ventilation, catecholamine, cooling, physiotherapy), the dietary carbohydrate-to-fat ratio, and genetic factors.[33–35] Its accurate assessment requires a measure by calorimetry, as predictive equations lack accuracy, especially cachectic, obese, or severely burned patients. Despite limitations related to the determination of energy expenditure by the exclusive estimation of energy from metabolism, the current model for establishing the global energy expenditure is the sum of the following components: basal metabolism, heat-generating ability of nutrients, thermoregulation, and physical activity. Due to the changes in REE over time, the relevance of its assessment at a specific time is questionable. The benefit of knowing the REE precisely to guide the bedside caloric prescription remains a widely debated topic.[36–38]

Use of Energy Substrates

Apart from any stress, the use of substrates is determined largely by the composition of the diet and the time since the last meal. The situation is dramatically different during stress conditions; the use of energy substrates is driven mainly by the different mechanisms previously described. Besides the use of substrates, macronutrient metabolism is also disturbed in stress conditions. The 3 phases are altered: GI absorption, intracellular metabolism, and substrate oxidation. The preferential use of carbohydrate and decrease in substrate oxidation characterize the acute phase. Differences in hormonal regulation partly explain the differential regulation of the use of macronutrients. In the acute phase, the protein metabolism is characterized by a muscle protein breakdown, during which amino acids will be eagerly picked up by other tissues that exceed the capacity for synthesizing acute phase proteins. The nitrogen balance is therefore very negative in these conditions. Regarding the carbohydrates, the postaggressive situation is associated with a substantial increase in glucose production by the liver, kidney, and perhaps the intestine from lactate, glycerol, alanine, and glutamine provided by other tissues.[39]

Carbohydrates. Once ingested, the long polysaccharides found in food or enteral solutions undergo an endoluminal digestion by salivary and pancreatic amylase. Oligosaccharides and disaccharides (lactose and sucrose) are again cleaved into monosaccharides by oligosaccharidases of the brush border of the jejunum. The activity of one of the major jejunal oligosaccharidases, lactase, is usually reduced after a period of fasting and/or critical situation.[40] That is why enteral nutrition

(EN) solutions intended for critically ill patients are generally depleted in lactose. After cleavage, the monosaccharides are actively transferred through the enterocytes and released into the circulation by a passive transport system.

Carbohydrates metabolism during stress. In stress situations, changes in the metabolism of carbohydrates include an increase in glucose production by the liver and a decrease in insulin-dependent glucose utilization. This inhibition of insulin effect is at least partially mediated by a reduction of the activity and/or translocation of glucose transporter type 4 (GLUT4), an insulin-dependent glucose transporter. The decrease in the use of glucose in insulin-dependent tissues is partially offset by an increased uptake and use of glucose in insulin-independent tissues, especially via glucose transporter type 1 (GLUT1), an insulin-independent glucose transporter that is activated by TNF-α and IL-1.[41] Increased glycolysis in insulin-independent tissues provides gluconeogenic substrates, such as pyruvate, usable by the liver and kidney. The liver as a substrate for glucose production also uses glycerol obtained from an accelerated lipolysis. Glucose is the preferred energy substrate during stress conditions and is able to provide 2 adenosine triphosphates (ATPs) after anaerobic glycolysis and 36 additional ATPs by the Krebs cycle when the mitochondria are fully functional.

Stress hyperglycemia. It has long been recognized that critically ill patients tend to develop stress-related hyperglycemia.[41] For many years, this was believed to be a part of the adaptive host response to critical illness and designed to provide high amounts of glucose to white blood cells and other obligatory glucose users. Hyperglycemia was believed to be a biomarker of the severity of illness. This view has been challenged in one interventional study where decreased blood glucose with insulin was associated with an improved outcome.[42] However, these findings were not confirmed in other studies.[43] In any case, the pathophysiology behind "stress hyperglycemia" is very different from type II diabetes. The etiology of type II diabetes is a combination of insulin resistance and secretory deficit of β cells of the islets of Langerhans. The plasma glucose concentration is typically increased in critical situations and generally referred to as stress hyperglycemia. Unlike type II diabetes, the development of stress hyperglycemia involves a series of complex interactions between some substances secreted (such as catecholamine, GH, or cortisol) and cytokines, causing both excessive and noninhibitable production of glucose by the liver and insulin resistance of the tissues where glucose uptake is insulin dependent. Those interactions could be assimilated as an adaptive response needed to promote survival during the acute phase.[32] The stress-related increase in hepatic output of glucose results from glycogenolysis and gluconeogenesis. Glycogenolysis is primarily triggered by catecholamines and perpetuated under the influence of epinephrine and cortisol. Gluconeogenesis is stimulated to a larger extent by glucagon than by epinephrine and cortisol. Among the numerous inflammatory mediators released in the acutely ill, TNF-α might promote gluconeogenesis by stimulating glucagon production. The increase in peripheral resistance is characterized by the inability of skeletal muscles and adipocytes to take up glucose, related to an alteration of insulin signaling and with downregulation of GLUT4.[44]

In experimental conditions, concentrations of glucose >300 mg/dL are clearly deleterious. New insights into the cellular mechanisms of glucose toxicity suggest a link among glucose, cytopathic hypoxia, and the production of reactive oxygen and nitrogen species.[45,46] Moreover, it is also important to note that an exogenous carbohydrate supply inhibits gluconeogenesis only partially, in contrast to the physiological situation.

Lactate use as an alternative substrate. The alteration of lactate metabolism is one of the main characteristics of the response to metabolic stress. Lactate is a substrate obtained from the reduction of pyruvate in anaerobic glycolysis. Under normal conditions, the production and removal of lactate are equivalent (1200–1500 mmol/d) and lead to a stable serum concentration around 0.8–1.2 mmol/L. Lactate is produced primarily by the brain, muscles, and the GI tract while its clearance is ensured for >70% by the liver.

Through the Cori cycle (which describes the conversion of lactate to glucose), lactate represents an alternative energy substrate, especially in stressful circumstances.[47] Growing data suggest this metabolic pathway is favored under stress conditions and that lactate per se is at least a useful if not an obligatory substrate used by organs and tissues during energetic crisis conditions and has been particularly demonstrated to fuel the heart and brain.[48,49]

Recommendations for clinical practice. The use of intravenous (IV) glucose maintenance solutions (50–100 g dextrose/d) has not been assessed prospectively but could represent an acceptable compromise to prevent hypoglycemia and severe hyperglycemia. Nutrition formulas usually contain 10–15 g carbohydrate per 100 mL (ie, 50%–60% of total energy intake), which is theoretically appropriate in healthy individuals and during stress as long as blood glucose is controlled.

Fats. The endoluminal cleavage of triglycerides in food and those incorporated in nutrition formulas for enteral gastric lipase turns them into diglycerides and free fatty acids (FFAs). As for carbohydrates, the absorption of fat from the GI tract is altered in critically ill patients: a recent study showed a 50% reduction in the absorption of long-chain fatty acids in mechanically ventilated critically ill patients compared with healthy controls.[50] A second cleavage by pancreatic lipase converts them into monoglycerides and fatty acids. After transient binding to bile salts, monoglycerides and FFAs pass through the membrane of enterocytes. They are then converted into triglycerides and form chylomicrons after binding to phospholipids and apolipoproteins.

Fats metabolism in stress. Unlike carbohydrates, fat use as energy substrate does not increase significantly during the early phase following an insult. Indeed, the conversion of fats into ATP requires both large amounts of oxygen and a preserved mitochondrial function. It is obvious that these conditions are hardly encountered in a stressful situation in which tissue hypoxia and mitochondrial dysfunction are common.

In stress conditions, endogenous triglycerides stored in the adipose tissue and exogenous triglycerides released from chylomicrons and other lipoproteins are avidly hydrolyzed to release FFAs and glycerol into the bloodstream. In contrast to physiological conditions, this increased lipolysis cannot be effectively prevented by the infusion of carbohydrates or exogenous fats. The oxidation of FFAs is increased in peripheral tissues while they are converted in a small proportion to ketone bodies in the liver. They are mostly reesterified to triglycerides and released into the bloodstream in the form of very low-density lipoprotein (VLDL). In fact, the production of FFAs from exogenous and endogenous triglycerides always exceeds their use, and plasma concentrations of FFAs are typically increased under stress. Since lipoproteins, including VLDL, can bind endotoxin and target it for degradation in liver parenchymal cells,[51] a rise in VLDL lipoprotein concentration may be, in part, a protective mechanism. During stress situations, low plasma cholesterol concentrations have been described, with concentrations of both low-density lipoproteins and high-density lipoproteins being decreased.[52] Septic patients admitted to the intensive care unit (ICU) with low concentrations of high-density lipoprotein or low-density lipoprotein had a higher risk of mortality than those with higher concentrations of these lipoproteins.[53,54] Some guidelines recommend IV lipid infusion in critically ill patients when enteral feeding is impossible.[55] However, excess rates of lipid infusion may be deleterious. Therefore, the rate of lipid infusion needs to be controlled and limited. Finally, fatty acid components of triglyceridemia are biologically active, and the precise composition of fat used in artificial nutrition support of critically ill patients may affect metabolic, physiological, and clinical outcomes.[56–58]

Proteins. Protein metabolism is a core part of metabolism, particularly in critical illness. Ingested polypeptides undergo metabolism in 2 steps: the first phase is endoluminal, and the second phase occurs in the intestinal mucosa. Gastric acidity enables protein denaturation, which is then more susceptible to the effects of gastric and pancreatic proteolytic enzymes. Nevertheless, gastric acidity is frequently reduced in critical conditions following the bile reflux and under the effect of prophylactic treatment of stress ulcer. Oligopeptides and amino acids cross the brush border, in which they are phagocytosed by enterocytes.

Proteins metabolism in stress. In critically ill patients, the rate of breakdown of endogenous proteins is systematically increased under the influence of hormonal and inflammatory mediators and exceeds protein synthesis capacity. The whole-body increase in degradation rate is to a large extent attributable to the elevated rate of protein degradation in skeletal muscle.[59] Muscle protein degradation rate in critically ill patients may be 3-fold higher than normal.[60] Three main routes for protein degradation are described: cytoplasmic free enzymes, the proteasome system, and the lysosomal system. All systems are activated in the critically ill upon the metabolic response to stress, causing excessive protein destruction and systematic muscle wasting. Sarcopenia is a characteristic feature of longstanding critical illness[61,62] and is one of the most devastating consequences of the metabolic response to stress, whose effects can still be present several years after injury.[63] Excessive amino acids released by the protein degradation are oxidized in the liver and muscle, and nitrogen is excreted by the kidneys in the form of urea and ammonium. During prolonged postaggressive situations, depletion of energy and protein reserves of the body that results from these adaptive mechanisms may worsen patient morbidity and mortality and at least delay the recovery and healing.[64–66]

The close connection between lean body mass and outcomes has fostered the idea that actions to attenuate the loss of lean body mass may be a good strategy to improve outcomes. To increase lean body mass, adequate nutrition is a necessary condition (but not sufficient) for malnourished but otherwise healthy individuals. In nonmalnourished and healthy adults, an increase in lean body mass can only be achieved by simultaneous physical activity and adequate nutrition combination. For patients undergoing severe stress, the response to feeding in terms of alterations in lean body mass is not sufficiently explored. The response to nutrition intake may differ from the nutrition status of the patient upon admission and between the different phases characterizing the metabolic response to stress. At present, it is reasonably well established that caloric substitution will give a lower whole-body protein loss compared with no caloric substitution. However, the optimal caloric intake in critically ill patients is a matter of intense debate. Indeed, several retrospective studies reported a positive correlation between the magnitude of the caloric debt and the rate of complications,[65,66] while others reported that the provision of 25%–66% of the recommended caloric intake was associated with the best outcome.[64,67] Similarly, some interventional trials reported a worse outcome for patients receiving the larger dose of calories (ie, 25–30) than the smaller dose (10–15 kcal/kg/d) during the first days of the stay in the ICU.[68,69] The uncertainty regarding the optimal caloric intake is reflected by important divergences between guidelines, especially regarding the timing of adding supplemental PN when enteral intake is deemed insufficient during the first 7 days of the ICU stay.[70,71]

Several studies have attempted to interfere with protein metabolism using pharmacological agents. In general, the multiple trials of hormone supplementation during the

hypermetabolic phase have not been crowned with success in terms of morbidity and mortality in intensive care patients. For example, the use of large doses of GH by its anabolic effects stimulates protein synthesis and reduces proteolysis but contributes to increased morbidity and mortality of patients in intensive care due to undesirable side effects.[72] In addition, small studies have explored high insulin doses,[73] anabolic steroids,[74] and β-blockers.[75]

Changes in Body Composition

Some changes in body composition are frequently found in severe conditions such as sepsis, for example, loss of lean body mass and the relative preservation of fatty tissue.[76] The risk of development of "malnutrition" is definitively influenced by the baseline nutrition status and by the severity and duration of the inflammation. Some inflammatory parameters, such as IL-6, are an integral part of the nutrition assessment score for intensive care patients (Nutrition Risk in Critically Ill [NUTRIC] score), which needs to be validated prospectively.[77] Recent clinical studies have shown an association between muscle mass measured by different techniques and survival of ICU patients.[78,79] Plank[80] reported the derangements in body composition of 33 patients (21 with trauma and 12 with peritonitis) over a 3-week period from soon after admission to the ICU. Massive total-body protein loss occurred, which was derived principally from proteolysis of skeletal muscle in the early catabolic phase with a later contribution from visceral organs. Another notable change is an increase in the extracellular fluid component in both groups of patients.

Behavioral Changes

Food intake is a complex behavior that ensures periodic intake of energy and substances involved in several homeostatic mechanisms. Practically, 3 steps can be distinguished: a preprandial phase, a prandial phase, and a postprandial phase. In critically ill patients, the preprandial phase is altered by loss of appetite, the prandial phase can be altered by the presence of swallowing disorders, and the postprandial phase can be characterized by impairment of gastric emptying, gut motility, and alterations of the feeling of satiety. Loss of appetite during critical illness is probably very common, even though not accurately reported. Although the underlying mechanisms are only partially understood, psychological factors and changes in gut hormones have been reported.[81,82]

Long-term psychological consequences of critical illness have been receiving more attention in recent years.[83,84] Apart from the disease itself, the ICU environment exposes patients to extreme stressors, including painful procedures, multiple medications, mechanical ventilation, and inability to communicate. Often patients cannot make the difference between reality and hallucination. These feelings throughout hospitalization in the ICU can cause depressive episodes, major anxiety, insomnia, and even panic attacks.[85]

Conclusion

In summary, stress during critical illness is associated with a 3-phase metabolic response. The different triggers include synergistic neurological, endocrine, inflammatory, and immune pathways. Despite major hopes regarding nutrition modulation, inhibition of inflammation and oxidative stress was not found beneficial and is currently not recommended. The clinical consequences of metabolic response to stress include the preferential use of carbohydrates during the acute phase; stress-related hyperglycemia; loss of fat and muscle mass, implying muscular weakness; and ultimately anorexia. In practice, excess calories can be detrimental in the acute phase while sufficient caloric intake is essential during the hypermetabolic and recovery phases as it provides the necessary elements for the replenishment of protein and energy stores. The following list summarizes the major points of this review:

- The timing of the metabolic response to stress is characterized by 3 phases: the acute phase, the hypermetabolic phase, and the recovery phase.
- Excess calories can be detrimental in the acute phase (maximum provision: 20 kcal/kg/d).
- Caloric intake matching energy expenditure is required during the hypermetabolic and the recovery phases. A caloric intake of 25–30 kcal per kilogram (two-thirds carbohydrates, one-third fats), a protein intake of 1.2–1.5 g/kg, and a calorie-to-nitrogen ratio of 100–150 are usually recommended.
- Monitor and adapt nutrition management in case of changes in body composition and behavior.

According to these therapeutic failures, a better understanding of the pathophysiological processes underlying stress metabolism should refine future recommendations for the nutrition and pharmacological management of postaggressive situations.

Statement of Authorship

O. Lheureux and J.-C. Preiser contributed to conception/design of the manuscript; contributed to the acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Invited Review

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Anti-Inflammatory Diet in Clinical Practice: A Review

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Mari Anoushka Ricker, MD[1]; and William Christian Haas, MD, MBA[1]

Abstract

Recently, there has been an increase in the research regarding the impact of acute and chronic inflammation on health and disease. Specific foods are now known to exert strong effects on inflammatory pathways within the body. Carefully selecting foods that are anti-inflammatory in nature while avoiding foods that are proinflammatory is central to an anti-inflammatory diet plan. Ultimately, the plan models a pattern of eating that (1) focuses on eating whole, plant-based foods that are rich in healthy fats and phytonutrients and (2) maintains a stable glycemic response. (*Nutr Clin Pract*. 2017;32:318-325)

Keywords

anti-inflammatory diet; fatty acids; Mediterranean diet; glycemic index; nutrition therapy

Inflammation is one of the many responses of the immune system used to defend the body from injury. Classically, inflammation has been defined according to the effects of capillary dilatation and leukocyte infiltration, causing redness, heat, pain, and swelling.[1] From an evolutionary standpoint, the inflammatory response is inherently protective, eliminating destructive agents and healing damaged tissue in a temporary, self-limiting manner. However, when noxious stimuli persistently confront the body and/or the inflammatory response fails to resolve, chronic inflammation ensues.

Unlike acute inflammation, chronic inflammation is often indolent, causing silent damage systemically throughout the body. The clinically used markers of acute inflammation (erythrocyte sedimentation rate, C-reactive protein [CRP]) may not be elevated in the early stages of low-grade inflammation.

Over time, as organ damage increases, chronic diseases become apparent. Several disease states have now been associated with chronic inflammation: diabetes mellitus, coronary artery disease, and asthma.[2-4] Although inflammation is not the sole factor driving these disorders, it is a process that is strongly influenced by nonpharmaceutical interventions, such as diet. The following review evaluates the effect of various foods on the inflammatory response, and it outlines key components of an anti-inflammatory diet plan.

Nutrient Effects on Inflammation

Carbohydrates

One of the primary dietary factors affecting inflammation is the consumption of refined, high glycemic–load carbohydrates. Glycemic load is defined as the quantity of carbohydrate ingested, multiplied by the rate at which that carbohydrate enters the bloodstream (ie, the glycemic index). Regular consumption of high glycemic–load carbohydrates results in chronic hyperglycemia, which, through varying mechanisms, increases the production of free radicals and proinflammatory cytokines.[5,6] In attempt to reduce elevations of blood glucose, the pancreas secretes insulin. Aside from shuttling glucose out of the bloodstream, insulin exerts influence on the enzymes delta-6 and delta-5 desaturase, rate-limiting enzymes controlling the conversion of linoleic acid into arachidonic acid.[7,8] Hence, the greater the insulin response to high glycemic–load carbohydrates, the more arachidonic acid produced. Of note, glucagon exerts an inhibitory effect on the desaturase enzymes, thereby reducing the production of arachidonic acid.[8]

Fats

Another important dietary contributor to inflammation is the level of ω-3 and ω-6 fatty acids (FAs) consumed. In general, ω-3 FAs are considered anti-inflammatory, while ω-6 FAs are proinflammatory. However, both FAs are essential nutrients within the body, and it is the ratio of these FAs that likely determines inflammation levels.[9] Although the precise ratio promoting inflammation is unknown, a ratio of ω-6:ω-3 FAs >10:1 is believed to be proinflammatory, which is likely 10-fold higher than the ratio that humans evolved eating.[10,11] Several studies, in fact, have demonstrated

From the [1]Center for Integrative Medicine, Department of Family and Community Medicine, University of Arizona, Tucson, Arizona, USA.

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Corresponding Author:
Mari Anoushka Ricker, MD, Center for Integrative Medicine, Department of Family and Community Medicine, University of Arizona, PO Box 245153, Tucson, AZ 85724-5153, USA.
Email: rickerm@email.arizona.edu

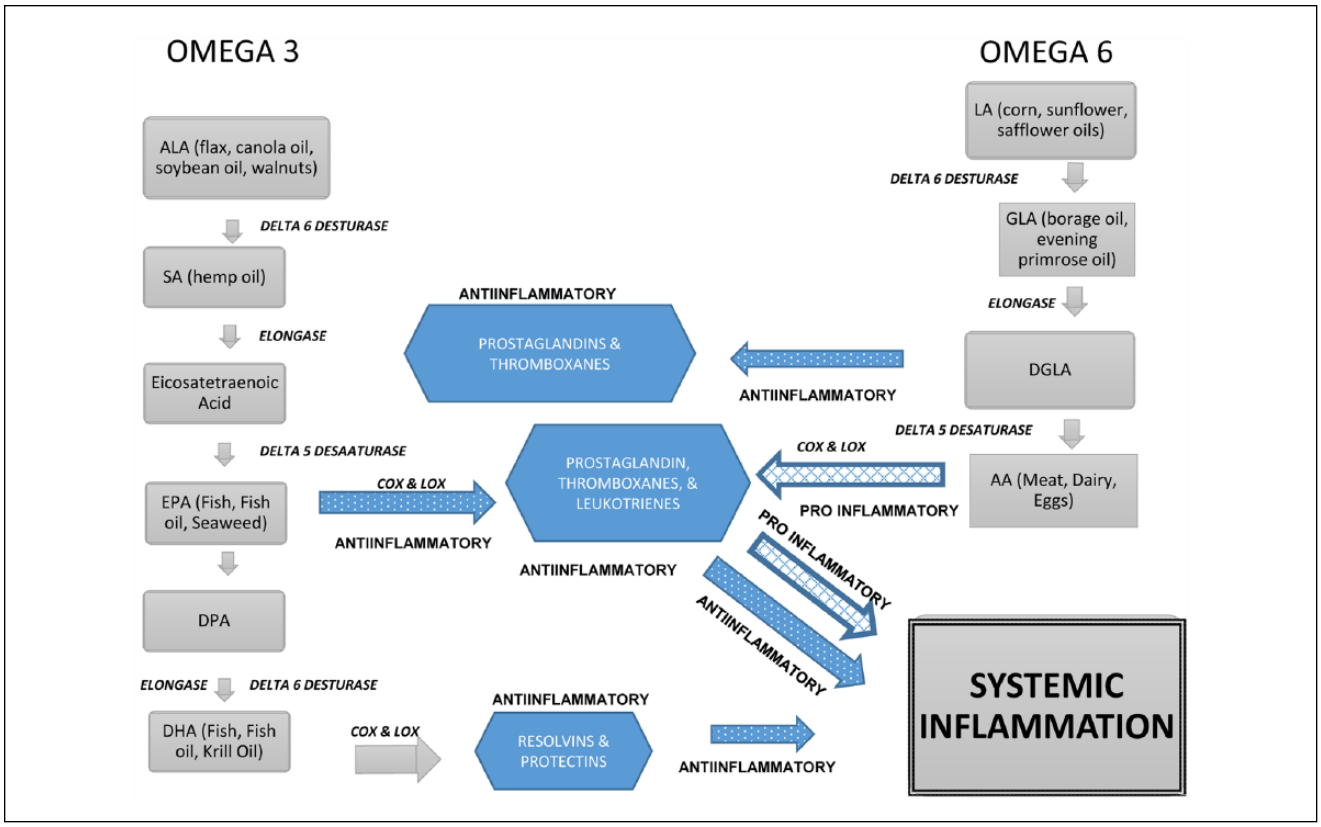

Figure 1. Fatty acid effects on systemic inflammation. AA, arachidonic acid; ALA, alpha-linolenic acid; COX, cyclooxygenase; DGLA, dihomo-gamma-linoleic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linoleic acid; LA, linoleic acid; LOX, lipoxygenase; SA, stearidonic acid.

a positive impact on various disease states (cardiovascular disease, rheumatoid arthritis, asthma) when the ω-6:ω-3 FAs ratio drops <5:1.[12]

A closer look at the metabolism of ω-6 and ω-3 FAs clarifies their effect on the inflammatory process (Figure 1). Linoleic acid, an ω-6 FA, serves as the precursor for a number of proinflammatory eicosanoids produced from arachidonic acid. As a result, the more ω-6 FAs consumed in the diet, the greater the propensity for increased levels of inflammation. ω-3 FAs, however, exert a number of anti-inflammatory effects. Opposite to the effect of insulin, ω-3 FAs inhibit the delta-6 desaturase enzyme, reducing the production of arachidonic acid in the first place.[8] Once arachidonic acid is produced, though, ω-3 FAs can indirectly limit the generation of proinflammatory eicosanoids by competing with arachidonic acid for space in the phospholipid bilayer of cell membranes.[13] Finally, ω-3 FAs can defuse existing inflammation by contributing to the production of a class of anti-inflammatory eicosanoids known as resolvins, which are believed to regulate activation and trafficking of polymorphonuclear leukocytes.[14,15]

In addition to the level of polyunsaturated fats consumed, trans FAs (TFAs) in the diet have a strong impact on inflammation. Present in small amounts of meat and dairy products from ruminant animals, TFAs are primarily consumed in foods prepared with partially hydrogenated vegetable oils (eg, bakery goods). The process of hydrogenation converts naturally occurring *cis* double bonds of unsaturated fats to trans double bonds, thereby producing a long-lasting solid fat with a high melting temperature. TFA consumption has well-established adverse effects on serum lipids, primarily due to the modulation of liver function and the metabolism of liporprotein.[16,17] However, evidence also suggests TFAs to be inherently proinflammatory. In clinical trials and observational studies, TFA consumption has been associated with increased markers of systemic inflammation, including tumor necrosis factor (TNF), CRP, and interleukin 6.[16,18,19] Moreover, TFAs may impair the metabolism of essential FAs involved in inflammatory pathways.[20]

Polyphenols

The shift away from freshly prepared foods to processed foods has reduced the consumption of plant-based phytochemicals, such as polyphenols. Although polyphenols are not considered an essential nutrient, mounting evidence suggests that they are

an important contributor to optimal health, partly through a reduction of inflammation.[21-23] The anti-inflammatory effect of polyphenols was initially attributed to their ability to neutralize free radicals, resulting from their structure of conjugated double bonds with a free hydroxyl group. Polyphenolic compounds may also increase endogenous antioxidant defense through the regulation of Nrf2, an important cellular redox transcription factor involved in phase 2 detoxification.[24] Beyond their antioxidant effects, polyphenols dampen the inflammatory response. Polyphenols activate gene transcription factors that inhibit the activation of NF-kB, an important transcription factor responsible for activating inflammation pathways.[25]

Caloric Intake

Beyond the impact of specific nutrient groups, chronic inflammation is affected by caloric intake. Excess caloric intake, particularly in sedentary individuals, results in increased adiposity. Adipose tissue is a metabolic active tissue that directly contributes to chronic inflammation through the release of proinflammatory cytokines, including TNF-α and interleukin 6.[26] As adipocytes enlarge, further inflammation ensues as a result of infiltration and activation of macrophages that release additional inflammatory cytokines.[27] A number of other proinflammatory alterations occur as a result of excess adipose tissue, including increased insulin resistance and sympathetic nervous system activation.[28,29]

In contrast to excess caloric consumption, calorie restriction with adequate nutrition intake has been shown to exhibit important anti-inflammatory effects. Reducing the number of adipocytes in the body through calorie restriction lowers the level of proinflammatory adipokines and cytokines.[30] The same reduction of fat cells also improves insulin sensitivity and reduces plasma glucose levels, thereby lowering the production of advanced glycation end products. The reduction of advanced glycation end products dampens the activation of pathways that would otherwise promote expression of adhesion molecules and chemokines, induce oxidative stress, and release inflammatory cytokines and growth factors.[31] Separate from its effects on adipose tissue, calorie restriction enhances endogenous corticosteroid production, promoting anti-inflammatory effects in the body.[32] Finally, calorie restriction may increase parasympathetic tone, contributing to the suppression of cytokine-mediated inflammation.[33]

Anti-Inflammatory Diet

Despite a growing awareness for the health benefits of an anti-inflammatory diet, a single universal definition does not exist. One of the first versions of an anti-inflammatory diet was published in 1995 in *The Zone Diet*, by Barry Sears, PhD.[34] The concept of designated macronutrient ratios and their impact on cortisol and insulin levels were key to his definition. In recent research, the Mediterranean and Okinawan diets have been identified as dietary patterns with anti-inflammatory properties.[35-37] As a result, the most commonly used definition of an anti-inflammatory diet currently incorporates aspects of both the Mediterranean diet and the Okinawan diet, in addition to recommendations for balancing macronutrient ratios. Beyond outlining a general dietary pattern, an anti-inflammatory diet incorporates the use of herbs, spices, and supplements that complement the overall dietary approach.[38-40]

The standard American diet provides a stark contrast to the beneficial components of an anti-inflammatory diet. Most Americans eat more red meat, less fish, more sugar and simple carbohydrates, and fewer fruits and vegetables than are included in the Mediterranean and Okinawa diets.[41] The Mediterranean diet, eaten by those living near the Mediterranean Sea, is high in vegetables, fruits, fish, and olive oil and includes moderate red wine intake.[36,37] The Okinawa diet, named after the southernmost Japanese prefecture, is also high in vegetable and fruit intake and lacking in dairy and red meat. In contrast to the Mediterranean diet, however, the Okinawan diet is much lower in overall fat intake[35] (see Table 1).

Vegetables and Fruits

An anti-inflammatory diet relies on vegetables and fruits to make up a large portion of the diet. Vegetables and fruits are lower in caloric density and abundant in beneficial nutrients, including vitamins, minerals, and phytonutrients. Generally, they should be eaten in large volumes, with every meal, and in a variety of colors and types. Vegetables and fruits contain large concentrations of polyphenols, giving them their characteristic colors yet, more important, providing their anti-inflammatory properties. Moreover, fruits and vegetables, especially the non-starchy varieties, are high in fiber, reducing their glycemic index relative to other carbohydrates.[39] An ideal anti-inflammatory diet should ultimately contain up to two-thirds of the total food volume in vegetables and fruits.[39] As discussed, many studies have shown that diets high in fruits and vegetables correlate with lower levels of inflammatory markers in the blood.[42,43]

In practice, an anti-inflammatory diet emphasizes eating more vegetables than fruits, due to the lower glycemic index of the former. Whenever possible, vegetables should be organic in variety, as they are lower in pesticides and possess higher levels of antioxidants than the conventional variety.[44] Additionally, efforts should be made to eat vegetables and fruits in season, when they are fresh, yielding more available nutrients and, thus, antioxidant properties, often at a cheaper cost. Many fruits and vegetables, however, retain and even enhance their nutrients when frozen, providing a good alternative when eaten out of season, as they are picked at peak ripeness. Most fruits and vegetables are then blanched and frozen immediately.[45] Vegetables can be easily prepared with small amounts of olive oil and anti-inflammatory spices (discussed later).

Protein Sources

Protein in an anti-inflammatory diet should be primarily plant based, with some sources of fish and small amounts of lean

Table 1. Comparison of Diet Components.

Diet	Standard American Diet	Mediterranean Diet	Okinawan Diet	Anti-Inflammatory Diet
Vegetables and fruits	Fewer vegetables	High consumption of vegetables and fruits	High consumption of vegetables: orange-yellow root vegetables, leafy green vegetables	High consumption of vegetables: large diversity, including variety of colors to increase phytonutrients
Protein source	Red meat	Fish	High consumption of legumes (soy)	Plant sources of protein: legumes, soy, nuts, and seeds
	Dairy	Legumes	Small to moderate amounts of fish	More fatty fish and some lean animal protein
		Nuts	Less meat	
Carbohydrates	Refined carbohydrates; high-fructose corn syrup and added sugar Fewer whole grains	Whole grains	Small amounts of rice and noodles Less sugar and fewer refined grains	Whole grains in small amounts, high fiber, reduced refined carbohydrates
Dairy	High-fat dairy sources	Low-fat dairy, such as yogurt	Less dairy	
Fats	Solid added fats, such as butter and sour cream	Olive oil as source of added fat	Lower fat overall	Olive oil for added fat source
Other features	Soda and added-sugar beverages	Moderate red wine intake	Moderate alcohol intake, green tea intake; broth-based soups	Spices: turmeric, garlic, ginger, and other anti-inflammatory herbs and spices
Cultural	Eating on the run, overeating	Highly social and connected eating experiences	Low caloric diet; highly ritualistic culture	Mindful eating approach; quality over quantity

natural meats.[46] The type of fat contained within the protein source is a central determinate in whether it is anti-inflammatory versus proinflammatory. Animal protein contains higher levels of ω-6 FAs, and an anti-inflammatory diet should include protein sources containing higher levels of ω-3 FAs.[47] When consuming animal protein, one should eat fresh-water fatty fish containing high levels of ω-3 FAs, including salmon, mackerel, halibut, sardines, and herring. Careful attention should be given to sourcing wild-caught fish while avoiding farm-raised fish, as wild-caught fish have higher levels of ω-3 FAs.[48,49] As with fish selection, beef produced from naturally grazing cattle have lower ω-6:ω-3 ratios as compared with conventional beef.[50] In addition to grass-feeding practices, organically produced dairy and meats have been shown to contain higher levels of anti-inflammatory ω-3 FAs versus their nonorganic counterparts.[51] Another important aspect of meat consumption includes the cooking method. Meats cooked at high temperature or charred produce heterocyclic amines and polycyclic aromatic hydrocarbons and create advanced glycation end products,[52,53] which are proinflammatory. Furthermore, the heterocyclic amines and polycyclic aromatic hydrocarbons have been shown to be mutagenic and to cause cancer in animal models.[54] Although a direct link to cancer has not been established in humans, epidemiologic studies have found strong associations with cancer among individuals consuming large amounts of meat cooked well-done or grilled.[55-57]

Although an anti-inflammatory diet permits the intake of some animal protein, plant-based proteins should predominate. Soy legumes, such as edamame, tempeh, or tofu, are an excellent source of plant-based protein. The phytonutrients, protein, and healthy fats in soy all contribute to its anti-inflammatory properties. In fact, soy has been shown to decrease the inflammatory markers interleukin 6, TNF-α, and CRP.[58,59] At the same time, intake of non–soy-based legumes has been shown to have an inverse relation to high-sensitivity CRP.[60] Phytoestrogens in soy, daidzein and genistein, contribute to soy's reduction in systemic inflammation.[61] Finally, mushrooms are a good source protein, containing polyphenols and other anti-inflammatory phytonutrients.[62,63] It is recommended that mushrooms are cooked, to reduce natural carcinogens, as well as to release more nutrients, as they have a very tough cellular structure that is softened with cooking.[64]

Carbohydrates

Although vegetables and fruits constitute the major source of carbohydrates in an anti-inflammatory diet, other carbohydrate types are incorporated. As in the Mediterranean and Okinawan

Table 2. Comparison of Sources of ω-6 and ω-3 Fatty Acids.[a]

Food	Serving Size	Calories	ω-6 Linoleic Acid, g	ω-3, g		
				ALA	EPA	DHA
Salmon, sockeye, cooked, dry heat	3 oz	133	0.16	0.05	0.25	0.48
Tuna in water, canned	3 oz	109	0.05	0.06	0.20	0.54
Egg, poached	1 large	72	0.78	0.02	0	0.03
Walnut, dry roasted	1 oz	180	9.93	2.38	0	0
Flax seed, ground	1 tbsp	37	0.41	1.6	0	0
Chia seed, dried	1 oz	138	1.7	5.1	0	0
Sesame oil	1 tbsp	120	5.6	0.04	0	0
Olive oil	1 tbsp	119	1.3	0.1	0	0
Canola oil	1 tbsp	124	2.6	1.3	0	0

ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
[a]Data based on https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/nutrient-data-laboratory/.

diets, whole grain carbohydrates with a low glycemic index are the mainstay for an anti-inflammatory diet. Consumers should choose their whole grains carefully, selecting grains with all their original parts present (bran, germ, and endosperm) and not the "refined" counterpart that strips out much of the nutrients. Moreover, grains that have been processed via the cracking or crushing should be limited due to their high glycemic index. Examples of whole grains include buckwheat, barley, rye, and wild rice. Most of these whole grains are also high in fiber, which has been shown independently to reduce inflammatory markers.[65-67]

Healthy Fats

One of the significant differences between an anti-inflammatory diet and other diets is the emphasis on so-called anti-inflammatory fats. These fats may be present within foods classically categorized as fruits, vegetables, or protein, but they may also be added to the diet through supplementation of ω-3 FAs. Cold-water fish is one of the protein sources with the highest levels of ω-3 FAs, particularly salmon, sardines, and anchovies. The ω-3 FAs in these fish are especially beneficial, as they come preformed in eicosapentaenoic acid and docosahexaenoic acid, negating the need for conversion within the body. As fish oil has been shown to be a potent inhibitor of inflammation at doses higher than what can typically be acquired in food, it can be added as a supplement to an anti-inflammatory diet. A common recommendation is 1000 mg of fish oil, 3 times per day.[68]

Some eggs are also fortified with docosahexaenoic acid, but controversy remains regarding the impact of eggs on chronic disease.[69,70] With regard to plant sources of fats, flax seeds are rich in alpha-linolenic acid, which is less anti-inflammatory than eicosapentaenoic acid and docosahexaenoic acid but is a good source of ω-3 FAs. Other plant sources of alpha-linolenic acid include chia seeds, walnuts, and hemp seeds (see Table 2). In addition to maximizing ω-3 fat intake, trans FAs, which are proinflammatory, should be avoided.[9,71] When oils or fats are used to prepare foods, olive oil (mostly a monounsaturated fat) is the best choice when used at low temperatures.[72] Other oils that should be avoided—as they are proinflammatory—include soybean, cottonseed, peanut, and corn oil.[73]

Additional Components

Tea and Alcohol

In addition to the macronutrients that are included in an anti-inflammatory diet, other beverages can enhance anti-inflammatory processes. Drinking tea instead of coffee or sugary beverages can add an anti-inflammatory benefit. Tea is made by infusing the dried leaves of the plant *Camellia sinensis* in near boiling water, which releases antioxidants and polyphenols that contribute to reducing systemic inflammation. Green, black, and white teas contain these beneficial phytonutrients, with green and white having the highest levels.[74,75] As with other foods, sourcing tea that is organically produced will reduce any unintended proinflammatory impact from toxins or pesticides.

Moderate intake of alcohol, up to 1 drink per day for women and 2 drinks per day for men, is a component of both the Mediterranean and Okinawan diets.[76] Large studies have shown the cardiovascular benefit of moderate intake of alcohol as well as a reduction in inflammatory markers.[77,78] Heavy drinking, in comparison, showed higher levels of markers such as CRP.[79] Additionally, individual components of alcohol, such as resveratrol in red wine, have anti-inflammatory benefits.[80] However, the importance of moderation should be highlighted given the detrimental impact of heavy drinking on health and well-being, including increased cardiovascular disease and rates of certain cancers.[81,82] Ultimately, the recommendation for moderate intake should be made on an individual basis.

Spices and Herbs

Many herbs and spices have an impact on inflammation similar to the other components of an anti-inflammatory diet and can enhance the overall anti-inflammatory effect when added. However, given that the doses of spices and herbs studied are quite high, including them as often as possible in an anti-inflammatory diet will increase the likelihood of impact on inflammation. Ginger and turmeric are the 2 herbs with the largest amount of data supporting their impact on inflammation. They inhibit IL-2, TNF-α, and IL-8, which are proinflammatory cytokines; they also inhibit leukotriene and prostaglandin synthesis.[83-87] Additionally, garlic, cayenne, and oregano have anti-inflammatory properties and should be added to food while preparing meals.[88]

Eating Patterns and Habits

Beyond the dietary pattern of food selection, the manner in which food is consumed influences inflammation and nutrient value. Reinforced by complex social behaviors of Western society, Americans eat too much, too quickly, and on the run. Eating slowly, mindfully, and in smaller amounts can decrease the impact of inflammation on the body. Portion control and smaller meals decrease hyperglycemia and, in the long run, obesity—both of which reduce systemic inflammation.[89] Cortisol is a marker of stress in the body, and eating slowly, with a mindful approach, has been shown to decrease morning cortisol levels.[90] Changing the manner in which food is consumed may be equally as important as the food itself.

Conclusion

Influenced by the Mediterranean and Okinawan dietary patterns, an anti-inflammatory diet has emerged from a growing knowledge about the proinflammatory and anti-inflammatory effects of food. Although the components of an anti-inflammatory diet have been evaluated individually, adherence to the overall dietary plan may yield the greatest benefit, as shown in studies of the Mediterranean diet.[91] As such, an anti-inflammatory diet should not be prescribed according to its isolated components. Moreover, a truly integrative anti-inflammatory approach to nutrition will focus on eating mindfully and in caloric balance to help decrease obesity. The definition of an anti-inflammatory diet will likely continue to evolve with further advancements in nutrition research.

Statement of Authorship

Both authors contributed to the conception/design of the review; contributed to the acquisition, analysis, or interpretation of the data; drafted the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Emerging Clinical Benefits of New-Generation Fat Emulsions in Preterm Neonates

Gregory Guthrie, PhD[1,*]; Muralidhar Premkumar, MBBS, MRCPCH[2,*]; and Douglas G. Burrin, PhD[1]

Abstract

Soybean oil–based intravenous fat emulsions (IVFEs) have been the predominant parenteral nutrition IVFE used in the United States for neonates over the past 45 years. Even though this emulsion has proven useful in supplying infants with energy for growth and essential fatty acids, there have been concerns over its composition in the development of several morbidities, ranging from sepsis to liver disease, bronchopulmonary dysplasia, and impaired neurodevelopment and growth. The exact mechanisms that drive these morbidities in preterm infants are multifactorial, but potential contributors include high ω-6 (n-6) fatty acid composition, low docosahexaenoic acid and antioxidant supplementation, and the presence of potentially harmful nonnutritive components (eg, phytosterols). To address these issues, new-generation IVFEs with various types and amounts of fat have been developed containing greater amounts of the medium-chain fatty acids, long-chain polyunsaturated fatty acid, docosahexaenoic acid, lower concentrations of ω-6 polyunsaturated fatty acids, supplemental vitamin E, and low or negligible amounts of phytosterols. This review examines the clinical outcomes associated with different morbidities of parenteral nutrition in neonates who have received either soybean oil–based or new-generation IVFEs and addresses whether the proposed benefits of new-generation IVFEs have improved outcomes in the neonatal population. (*Nutr Clin Pract*. 2017;32:326-336)

Keywords

soybean oil; fish oils; medium chain triglycerides; olive oil; parenteral nutrition associated liver disease; bronchopulmonary dysplasia; sepsis; neurodevelopment; premature infants; intravenous fat emulsions; parenteral nutrition

Infants who are unable to feed with diagnoses such as extreme prematurity and short bowel syndrome following congenital or acquired gastrointestinal conditions are now able to survive mainly due to the availability of parenteral nutrition (PN). PN consists of amino acids, glucose, fats, electrolytes, minerals, and vitamins balanced to meet nutritional need. The fat component of PN serves as a source of nonglucose energy, to avoid hyperglycemia from excess glucose load, and to prevent essential fatty acid deficiency. The use of intravenous fat emulsions (IVFEs) based on soy oil for PN was implemented, as they are high in the essential ω-6 (n-6) polyunsaturated fatty acid (PUFA) linoleic acid and contain moderate amounts of the essential ω-3 (n-3) PUFA α-linolenic acid.

In the United States, Intralipid (Fresenius Kabi, Friedberg, Germany), a soy oil–based IVFE (SOFE), has been the predominant IVFE used for preterm infants for the past 45 years. While this emulsion has been very effective in reducing overall mortality, concern has recently developed whether this emulsion is contributing to common morbidities associated with preterm infants receiving PN. In preterm infants, there is strong evidence that preformed n-3 PUFA docosahexaenoic acid (DHA) is necessary for brain and retinal development.[1,2] In addition, there are concerns about the proinflammatory effects of n-6 PUFAs.[3] The presence of nonnutritive phytosterol compounds in SOFEs has also come under scrutiny for their potential role in suppressing gene expression pathways in bile acid homeostasis.[4] Inflammation and bile acid pathway dysregulation are associated with the morbidities of PN-associated liver disease (PNALD), sepsis,

From the [1]USDA/ARS Children's Nutrition Research Center, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Baylor College of Medicine, Houston, Texas; and the [2]Section of Neonatology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas.

*Both authors contributed equally to this work.

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Corresponding Author:
Douglas G. Burrin, PhD, Children's Nutrition Research Center, 1100 Bates St, Houston, TX 77030, USA.
Email: doug.burrin@ars.usda.gov

bronchopulmonary dysplasia (BPD), and impaired growth and neurodevelopment in preterm infants. Following the advent of SOFEs, second- and third-generation IVFEs have been in development over the last 2 decades that consist of combinations of fish oil, medium-chain triglycerides (MCTs), and olive oil, either as separate emulsions or in combination. These new-generation IVFEs have higher n-3 PUFAs and lower content of phytosterols and may be well suited as fat sources for preterm infants.

This review provides a brief overview of the clinical experience with the currently available IVFEs. The following sections summarize the current clinical literature on the most common morbidities associated with PN administration, the potential mechanisms of action, and the impact of new-generation IVFEs on incidence of these morbidities.

IVFEs

In 1929, Burr and Burr were the first to describe the essentiality of fat in the diet when they described features of essential fatty acid deficiency in their laboratory animals.[5] In 1968, Douglas Wilmore and Stanley Dudrick gave intravenous nutrition to a 2300-g infant with intestinal atresia for a period of 44 days and demonstrated improvement in growth.[6] Soon thereafter, they published a case series of 18 infants with gastrointestinal conditions, including surgical diagnoses, who were supported with PN for up to 400 days.[7] The parenteral solution administered in these landmark studies did not contain any IVFE, as none were available, so plasma was administered to supply essential fatty acids. Following this, Benda and Babson published their experience with 14 preterm infants weighing <1251 g who were safely given PN for a maximum period of up to 3 weeks.[8]

In the United States, Intralipid (SOFE) was first approved in 1972 for general use. To date, Intralipid remains the most commonly used fat source for PN and is derived from 100% soybean oil rich in n-6 PUFA. Apart from Intralipid, ClinOleic (olive oil–based IVFE [OOFE]; Baxter, Deerfield, IL) is another IVFE approved by the Food and Drug Administration for use in the United States; it is composed of 80% olive oil and 20% soybean oil (SO). Since the 1990s, Omegaven (Fresenius Kabi; fish oil–based IVFE [FOFE])—a IVFE derived entirely (100%) from fish oil rich in n-3 PUFA—has been increasingly used across the United States, strictly under Food and Drug Administration–approved compassionate use protocols for the treatment of PNALD. Other fat preparations that have been used in the United States and elsewhere include Lipofundin (50% MCTs and 50% soybean oil; B Braun, Philippines; coconut oil–based IVFE [COFE]), Lipidem (50% MCTs, 40% soybean oil, and 10% fish oil; B Braun; 3 oil–based IVFE [TOFE]), and newer-generation multicomponent IVFEs, such as SMOFlipid (30% soybean oil, 30% coconut oil–derived MCT, 25% olive oil, 15% fish oil; Fresenius Kabi; mixed oil–based IVFE [MOFE]). As of 2016 in the United States, SMOFlipid has been approved for use in adult patients but is not yet approved for pediatric use.

IVFEs and PNALD

In 1971, just 3 years since the first use of PN in infants, Peden and colleagues reported the death of an infant receiving PN who had developed liver failure and showed signs of cholestasis.[9] Five years from the first description of PN in infants, Touloukian and Downing described 3 of 18 infants who succumbed to various complications following PN, including cholestasis.[10] Over the next 2 decades as the association of liver disease with use of PN grew stronger, suspected etiologies included hyperglycemic load, deficiencies of various amino acids and trace elements, the fat component of PN, and free radical injury following exposure to light. Allardyce observed that the majority of patients who received higher doses of SOFE developed cholestasis, whereas those who received lower doses were spared from it, thereby suggesting a dose-dependent relationship between SOFE and cholestasis.[11] Results originating from laboratory animal studies further strengthened the link between the fat component dose of SOFE and PNALD.[12] Over the next 2 decades, several components of SOFE have been implicated in the pathogenesis of PNALD, including its predominant n-6 PUFA profile, high phytosterol content (particularly the stigmasterol), and low α-tocopherol levels.

PNALD is a complication of the liver in infants receiving PN. PNALD includes the biochemical and histologic alterations representing cholestasis, elevation of transaminases, and alteration of synthetic functions of the liver. The common serum biochemical markers of PNALD are an elevated conjugated bilirubin (CB) >2 mg/dL along with elevations in transaminases. The use of PN in modern neonatal intensive care units is common, as demonstrated by Christensen et al, who showed that nearly 70% of the 10,000 infants in their neonatal intensive care units received PN at some point and 21% of them for >14 days.[13] In the same report, PNALD was reported to be more common with immaturity and lower birth weights, longer duration of PN, and surgical gastrointestinal conditions.[13] The pathogenesis of PNALD is complex and multifactorial. Apart from exposure to PN, several other risk factors contribute to the pathogenesis of PNALD, such as absence of enteral feeds, prematurity, sepsis, states of inflammation (eg, necrotizing enterocolitis), gastroschisis, gastrointestinal surgery, and hypoperfusion injury, as seen in the presence of patent ductus arteriosus. Studies have suggested that an exposure to PN for a period as short as 2 weeks can induce PNALD in such high-risk population of infants. Prior to the widespread use of currently practiced interventions to treat PNALD, such as fat-lowering strategy and use of FOFEs, infants whose CB was >10 mg/dL had a nearly 40% chance of death or a liver transplant.[14]

Following the discoveries of the associations of PN with liver disease, several strategies were adopted to limit and reverse the damage inflicted by PN. These strategies included cycling of PN and use of choleretic agents, such as

ursodeoxycholic acid and cholecystokinin, all of which yielded very limited success.[15-17] One strategy that has been more effective in limiting liver disease is the fat-lowering strategy, where SOFE is given at a reduced dose of 1–1.5 g/kg/d instead of the regular dose of 3–3.5 g/kg/d. Even though the association of lower fat dosages with better liver health was first described by Allardyce,[11] rediscovery of the same association by Cavicchi et al a decade later renewed interest in this strategy.[18,19] It was noted that that those adults who received a smaller dose of fats had better outcomes and fewer liver-related complications. This practice was later adopted in the treatment of PNALD in the pediatric population with better but still suboptimal results.[20,21]

Gura et al described their experience with 2 soybean-allergic infants with short bowel resections who subsequently developed essential fatty acid deficiency and PNALD. Treatment with Omegaven in these infants resulted in not only reversal of cholestasis but also of essential fatty acid deficiency.[22] Since then, several institutions across the United States have successfully treated >1000 infants of PNALD with FOFE using compassionate use protocols.[23,24] In spite of the reported improved outcomes with the use of FOFE, a significant proportion of clinicians are skeptical about its purported benefits. Following the initial reports, FOFE has always been used in a dose of 1–1.5 g/kg/d, the same low-fat dosage at which several groups have shown similar liver-protective actions even with the use of SOFE. This and the absence of rigorous randomized controlled trials (RCTs) comparing the effectiveness of SOFE with FOFE in the resolution of PNALD have been the major criticisms against the supposed beneficial effects of FOFE.

In an attempt to address these deficiencies, a recently concluded RCT in infants compared the effect of FOFE and SOFE in the prevention and treatment of PNALD in which both IVFEs were given at a dose of 1.5 g/kg/d. Though the study failed to show any difference in the reversal of PNALD and was terminated prematurely, the rate of rise for CB and alanine amino transferase was lower in those infants who received FOFE. It was also noted that the infants in the FOFE group appeared to have better tolerance to enteral feeds.[25] Nehra et al conducted a double-blind RCT comparing FOFE and SOFE in neonates for prevention of PNALD, both given at a dosage of 1 g/kg/d. By the time that the low incidence of PNALD in both groups forced the investigators to end the study earlier than they had planned, the incidence of PNALD in the 2 groups was not significantly different.[26] The limitation of these 2 aforementioned studies is that they were conducted with relatively low-fat infusion rates resulting in low overall rates of PNALD. Several single-center RCTs have been conducted comparing the effects of SMOFlipid (MOFE) with SOFE, but none of these studies showed a difference in any of the biochemical indices suggestive of PNALD between the groups.[26-29] In one such study, Goulet et al compared the effects of MOFE with SOFE in pediatric patients receiving home nutrition and failed to show any benefits in terms of prevention of treatment of PNALD in these children.[30] In another study, 5 IVFEs—SOFE, MOFE, COFE, TOFE, and OOFE—were studied in infants with birth weight <1250 g. The rates of cholestasis were not only similar but also low across all treatment arms.[31]

All these single-center RCTs have been plagued by lower rates of cholestasis, thus being inadequately powered to address PNALD as a primary outcome in assessing the treatment with IVFE. Though the obvious solution to this issue would be to perform large multicenter RCTs, studies of this scope are lacking in current literature. To overcome this limitation and to synthesize meaningful information from the available small-scale studies, several meta-analyses have been conducted to study the effect of IVFE in the prevention and treatment of PNALD.

A recent meta-analysis was published comparing the use of FOFE with non-FOFE, assessing its efficacy in the prevention and treatment of PNALD in neonates. FOFEs included Omegaven, SMOFlipid, and Lipidem; non-FOFEs included Intralipid, Lipofundin, and ClinOleic preparations. The criteria for inclusion in this meta-analysis were less stringent, as it included case-control and prospective and retrospective cohort studies. In spite of these lenient criteria, only 7 studies fulfilled the requirements: 3 of which involved 93 subjects and addressed reversal of PNALD, while the other 4 involved 1012 subjects and addressed prevention of PNALD. The analyses suggested that the use of FOFE was more likely to reverse PNALD (odds ratio: 6.14, 95% CI: 2.27–16.6, $P < .01$) but failed to show any benefit of FOFE in prevention of PNALD. Still, the use of Omegaven was associated with near-significant trend toward decreased development of PNALD (odds ratio: 0.13, 95% CI: 0.02–1.03, $P = .05$).[32]

In the recently concluded Cochrane meta-analysis, with more stringent inclusion criteria, randomized or quasi-RCTs in preterm infants compared newer alternative IVFEs with SOFE. Various alternative IVFEs were studied in these 15 trials—including MCTs/long-chain triglycerides, MCTs and olive/fish/soy oil, MCTs and fish/soy oil, olive/soy oil, and borage/soy oil—in comparison with SOFE. There were no studies that compared 100% FOFE (Omegaven) with SOFE. Apart from 1 study in which alternative IVFE showed a decrease in stage 1 and stage 2 retinopathy of prematurity, there were no other benefits attributed to their use. It was concluded that based on the level of evidence presented in this review, the use of alternative IVFE, including FOFE, over the current standard of SOFE was not supported.[33]

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition performed a meta-analysis aiming to study the pathogenesis of PNALD.[34] This meta-analysis included 23 studies involving neonates and older children with either short-duration (<4 weeks) or long-term use of IVFE. This meta-analysis failed to show any beneficial effects with the short-term use of multicomponent fish oil containing IVFEs over the use of Intralipid. A meta-analysis of the long-term use

of multicomponent IVFE in the pathogenesis of PNALD could not be performed because of the paucity of studies. However, in one of the studies included in this meta-analysis, the long-term use of multicomponent FOFE was associated with some benefit.[26] Noncholestatic infants with intestinal failure who received multicomponent fish oil–based fat emulsion over prolonged periods exhibited a reduction in CB levels.

IVFEs and Sepsis

The actions of n-3, n-6, and n-9 PUFAs include wide-ranging effects on cell membrane structure and function, eicosanoid signaling, nuclear receptor activation, and fat metabolism. These PUFAs have been shown to modify leucocyte activity by altering (1) neutrophil, monocyte, and macrophage migration; (2) leucocyte adhesion to the endothelium; and (3) T-cell proliferative capacity to antigenic stimuli. n-6 PUFA (arachidonic acid and linoleic acid) metabolites—such as cyclooxygenase-derived prostaglandin-E2 and lipoxygenase-derived leukotriene B4—are predominantly proinflammatory, whereas n-3 PUFA–derived metabolites (eg, PG-E3, leukotriene B5) are predominantly anti-inflammatory in their actions. n3-PUFAs also generate protectins, D-series resolvins and maresins, and E-series resolvins that further extend their anti-inflammatory profile. n-3 PUFAs also act at the transcriptional level, thereby inhibiting activation of NF-kB and decreasing the production of various inflammatory cytokines such as tumor necrosis factor alpha and interleukins 1β, 6, and 8.[35,36] Because of these broad proinflammatory and anti-inflammatory effects on the inflammation pathway conferred by their predominant n-6 or n-3 PUFAs, the IVFEs have been thought to alter the risks of sepsis in infants who receive them.

Sepsis independently alters the profile of fat metabolism in critically ill infants. Patients with sepsis have elevated levels of plasma free fatty acids even in the absence of IVFEs, due to enhanced lipolysis from adipocytes, increased de novo lipogenesis in the liver, and decreased muscle fatty acid oxidation. This imbalance in fat metabolism is exacerbated by exogenous therapies used in critically ill infants, such as vasopressors (epinephrine and norepinephrine) and heparin, which activates lipoprotein lipase. Sepsis has also been shown to impair the ability of a premature neonate to handle intravenous fat load, as evidenced in infants with septicemia, in whom a higher mean serum triglyceride and free fatty acid levels are observed.[37] This state of dyslipidemia is exacerbated in the presence of morbidities such as growth restriction and prior liver dysfunction.[38] In states of sepsis, neutrophils exhibit decreased responsiveness to antigenic stimulation, secretion of leukotriene B4, and generation of platelet-activating factor and phosphatidylinositol.[39] As mentioned, various PUFAs also serve as substrates for products of inflammation with pro-inflammatory and anti-inflammatory profiles. Due to this extensive and complex interaction between sepsis and fats, it has been hypothesized that the use of IVFEs alters the risk of sepsis in neonates and infants.

In a retrospective case-control study performed in nearly 900 infants in neonatal intensive care units, the administration of IVFEs was shown to have a strong association with coagulase-negative staphylococcal bacteremia even when corrected for other risk factors. Those infants who received IVFEs were noted to have 5.8-times increased odds (95% CI: 4.1–8.3) of hospital-acquired coagulase-negative staphylococcal bacteremia.[40] In a study conducted in 40 premature infants with bloodstream infections, the dose of MOFE was compared with time taken for bacterial clearance. The experimental dose of MOFE, involving a restricted dose of 1 g/kg/d, was associated with significantly rapid clearance of bacteremia and reduction in antibiotic use duration in comparison with a standard dose with increases up to 3.5 g/kg/d. This study proposed that the protective effect of this MOFE is perhaps restricted to lower doses of fat load.[41]

Beken et al studied the effects of MOFE, in comparison with SOFE, in 80 very low birth weight (VLBW) infants with retinopathy of prematurity as their primary end point and showed that the rate of sepsis, a secondary outcome in this study, was no different between the groups.[27] Similarly, there were no significant changes in the rate of late-onset sepsis when D'Ascenzo et al compared various doses of MOFE and SOFE with an intention to study fat tolerance as the primary outcome.[42] Savini et al extended the comparison by studying the effect of 5 IVFEs—SOFE, MOFE, COFE, TOFE, and OOFE—in 150 infants with birth weight <1250 g. While the primary outcome was the plasma phytosterol levels, rate of sepsis (included as a secondary outcome) was not different across these regimens of fat preparations.[31] Similarly, several studies have been performed regarding VLBW infants that compared the effects of MOFE with SOFE, albeit with different primary outcomes, and they have failed to show superiority of one fat emulsion over the other in the prevention of sepsis.[29,43]

All of these studies were limited by smaller numbers of subjects and were inadequately powered to study sepsis as a primary outcome. A recent meta-analysis assessed the effects of early initiation of fat therapy on the general well-being of VLBW infants and compared the actions of SOFEs with non–soybean oil based fat emulsions. This included 2 studies in which SOFE was provided within the first 48 hours and compared with a delayed initiation[44-46] and 3 studies that compared SOFE with MCTs/long-chain triglycerides,[46] MOFE,[43] and OOFE.[47] This analysis showed trends toward decreased incidence of sepsis in infants who received IVFEs that were not purely soybean oil based (relative risk: 0.75, 95% CI: 0.56–1.00), thereby suggesting a protective effect of non–soybean oil based fat emulsions against sepsis in VLBW infants.[48]

IVFEs and BPD

BPD is a complex sequence of lung development, injury, and repair that is initiated by an in utero insult, postnatal management,

and aberrant lung tissue repair mechanisms.[49,50] The diagnosis of the disease is based on breathing abnormalities that arise from injury to the lung parenchyma with decreased microvascular development, alveolar septation, and airway injury.[49] Historically, BPD has been clinically assessed by various criteria including an oxygen requirement at 36 weeks corrected postmenstrual age in VLBW infants[51] and a more rigorous definition of preterm infants <32 weeks requiring supplemental oxygen at 36 weeks postmenstrual age or preterm infants >32 weeks requiring supplemental oxygen >28 days but <56 days postnatal age.[52] Chronic lung disease (CLD)/BPD is of considerable concern due to the long-term effects on growth failure[53-55] and impaired neurodevelopment.[56-58] The mechanisms by which IVFE can contribute to BPD are not fully understood; however, some potential targets include impaired pulmonary oxygen diffusion,[59,60] fat agglutination leading to embolism,[61] oxidant stress,[62,63] and inflammation.[64]

Preterm infants are more susceptible that term infants to oxidant stress,[65,66] and high oxidant stress in preterm infants has been correlated with CLD/BPD.[67] The higher oxidant stress in preterm infants is likely due to lower levels of glutathione as compared with term infants, which leads to impaired redox potential.[68] Further connection to this is the observation that levels of glutathione are typically lower in male preterm infants than females, and they have a tendency for a greater incidence of BPD.[68,69] SOFE is prone to oxidation, which can generate fat hydroperoxides, especially in the presence of a high concentration of oxygen from mechanical ventilation, which could facilitate increased oxidant stress in the preterm infant.[70]

Hammerman and Aramuro were the first to show, in a small cohort (n = 43) of VLBW neonates, that by withholding IVFE for 5 days, they could decrease the incidence rate of BPD.[71] Cooke gave further strength to the concept of IVFE-induced BPD by examining >650 preterm infants born ≤30 weeks, out of which 195 infants received supplemental oxygen for >4 days and lived to 28 days.[72] From the infants receiving supplemental oxygen, 87 developed BPD. There was a strong association with the infants developing BPD and receiving fats during their first 21 days. These early studies presented a strong case for not only the administration of IVFE leading to BPD but that specifically early administration of fat could be the driver of the disease. However, more recent studies have not supported that idea. Alwaidh et al looked at 64 VLBW preterm infants who received fat at 5 or 14 days after birth and saw no difference in BPD incidence.[73] Ibrahim et al administered earlier PN at 2 and 48 hours following birth and did not increase the incidence rate of BPD in VLBW infants either.[74] A 2012 meta-analysis by Vlaardingerbroek et al examined 4 clinical studies stratified by IVFE administration initiated before 2 days and after 2 days and also failed to see any overall effect on the incidence of BPD/CLD (relative risk: 0.88, 95% CI: 0.68–1.14).[48] The results of these later studies suggest that the very presence of parenteral fat is likely a risk factor for BPD rather than any specific time point when it is administered. In support of this, infants who receive >50% of their total caloric intake from enteral feeds do have a lower incidence of BPD/CLD.[75]

Fats such as OOFE contain much higher concentrations of monounsaturated fatty acids, making them more stable and less likely to undergo peroxidation as compared with soy-only emulsions. IVFEs that contain fish oil (FOFE and MOFE) contain n-3 PUFAs, DHA, and eicosapentaenoic acid, which are at risk for fat peroxidation, but are supplemented with 500 μmol/L of synthetic all-rac-α-tocopherol to prevent oxidation. Several small studies examined the rate of oxidation of OOFE in preterm infants. Pitkanen et al measured the effect of fat peroxidation in VLBW infants with respiratory distress. This small study (n = 13) used a short-term 3-hour administration of VasoLipid, an MCT-soy emulsion, and compared fat oxidation by pentane exhalation with ClinOleic. There were no differences on the extent of fat peroxidation by the administration of either IVFE.[76] A similar result of no effect on fat peroxidation was seen in a longer-term study by Koskal et al on VLBW infants administered OOFE or SOFE following 7 days.[77] This study also looked at the outcome of BPD in the infants. There was a significantly lower incidence of BPD, with only 31% of infants receiving OOFE versus 69% of infants receiving SOFE. The beneficial effects of OOFE compared with soy-based emulsions in ELBW infants have not held up in subsequent studies.[31,78] However, the trend for these studies suggests that in extremely low birth weight (ELBW) and VLBW preterm infants, administration of monounsaturated-rich olive oil containing fats does not appear to improve the outcomes on BPD or have much effect on oxidant stress.

Fish oil containing IVFEs could represent a far better option for the prevention of BPD in preterm infants as compared with monounsaturated-rich fat emulsions. As mentioned, FOFE are supplemented with vitamin E to reduce fat peroxidation while in storage and to limit oxidative stress once infused into infants. DHA also has well-established anti-inflammatory properties that may have a role in reduced lung inflammation.[79] Of particular benefit to very preterm infants, DHA could aid in lung maturation through activating peroxisome proliferator-activated receptor gamma.[80,81] DHA has an important role in the prevention of CLD in infants, as low DHA levels strongly correlate with a high CLD incidence rate.[82] This finding suggests that DHA supplementation could reduce the incidence of CLD. Two studies found that the administration of MOFE for 8 and 14 days to VLBW preterm infants led to reduced markers of oxidative stress when compared with control IVFE lacking fish oil and vitamin E supplementation.[43,83] In a prospective observational study by Skouroliakou et al, the administration of MOFE in place of SOFE led to a significantly lower incidence of BPD in VLBW infants (6% vs 23%, respectively) but did not affect BPD outcomes in low birth weight infants.[84] Results in low birth weight are mostly due to the low overall incidence of BPD in this population of neonates. However, this research

group has a recent 2016 randomized controlled double-blind study of 71 VLBW preterm infants that does not show a significant difference in BPD incidence between MOFE and SOFE (24% vs 46%, respectively).[85] This outcome may be due a lack of statistical power as their prospective study had a sample size of 129 neonates and their current study only had 51 neonates. However, studies by Savini et al, Vlaardingerbroek et al, Deshpande et al, and D'Ascenzo et al also failed to see a difference in BPD outcomes in VLBW infants receiving MOFE compared with SOFE.[28,29,31,83] D'Ascenzo et al administered MOFE and SOFE at 2.5 and 3.5 g/kg/d and saw no difference at either concentration nor a dose-related effect in BPD.[28] Pawlik et al administered OOFE or a 50:50 mix of OOFE:FOFE emulsion on a mixed VLBW/ELBW population of preterm infants.[86] The OOFE group had a 27% incidence rate of BPD, compared with a 23% incidence rate in the OOFE/FOFE mix group, which was not significantly different. These incidence rates also fall within the ranges seen for the development of BPD in studies using SOFE. The most recent meta-analysis from the Cochrane database by Kapoor et al fails to show a treatment effect of new-generation IVFE compared with SOFE for BPD.[33] The current data are mixed on the beneficial effect from using a different type of IVFE in parenteral formulas for the prevention of BPD. Fewer studies show positive effects overall. Larger multicenter trials with the treatment of MOFE are needed to draw definitive conclusions.

Pulmonary inflammation is a major contributor to the development of BPD.[64] Inflammation from IVFE is believed to be derived from the high n-6 PUFA content present in SOFE. As discussed in detail in this review, the n-3 PUFAs in new-generation IVFEs (FOFE and MOFE) are thought to be anti-inflammatory. The most studied aspect of this has been with allergic response through maternal supplementation with DHA, with the best example being the DINO study (Docosahexaenoic Acid for the Improvement of Neurodevelopmental Outcome in Preterm Infant Trial). Lactating mothers were supplemented with DHA to increase milk DHA concentration to 1% of total fatty acids. Manley et al analyzed data from this study and found that preterm males ≤1250 g had reduced incidence of hay fever.[87] However, this effect was not seen in preterm females or low birth weight males. There were also no differences in other forms of allergic response, including asthma, eczema, or food allergies. There have also been more direct findings that DHA supplementation during pregnancy can lead to downregulation of interleukins 4 and 13 in neonates.[88,89] There is limited research directly showing an effect of n-3 PUFAs on an infant's inflammatory response as it pertains to lung function. An RCT by Deshpande et al saw increases in inflammatory markers (interleukins 6 and 8) in VLBW preterm infants receiving SOFE day of life 30, whereas MOFE-administered infants had no change or a slight nonsignificant reduction in both cytokines.[83] The incidence of BPD failed to reach a significant difference between groups; however, the SOFE group had a 46% BPD incidence and the MOFE group, a 24% BPD incidence. A better-powered study could have seen benefit from MOFE treatment.

IVFEs and Neurodevelopment

Preterm infants, especially ELBW preterm infants, are at a higher risk of having poor neurodevelopmental outcomes.[90-97] DHA incorporation into the brain is necessary for cell signaling through altering fluidity of lipid rafts,[98] modulating sodium and calcium channels in neurons,[99] and neurogenesis.[100] In addition to brain function, DHA serves as a neuroprotective molecule through generation of bioactive compounds such as neuroprotection D1.[101] The fetal brain increases to a total fat content of 1.45, 4.74, and 8.79 g at 25, 35, and 40 weeks, respectively.[102] This increase in brain fat is accompanied by an increase in total DHA content to 102, 356, and 682 mg at 25, 35, and 40 weeks, respectively. Interestingly, this DHA increase maintains the total DHA content in the brain to 23% of all bodily DHA stores. The main source of DHA during fetal growth is through maternal placental transfer, so preterm birth represents an abrupt loss of preformed DHA for the infant. As the accretion rates show, preterm infants born at <35 weeks are at risk for a severe shortage of DHA to reach levels seen at 40 weeks. In addition to brain accretion of DHA, adipose tissue undergoes a selective increase in DHA during the final trimester.[102] The loss of this DHA reservoir can be seen by the first postnatal week where serum DHA drops from 7 to 4.5 mol%.[82] Preterm infants do show some capacity to synthesize DHA from precursor fatty acids, but it is limited and decreases over the first 7 months of life.[103] So, the need for appropriate supplementation of preformed DHA is potentially very important for long-term outcomes in this infant population.

Most studies looking at the effects of DHA use cognitive assessment tools to determine efficacy. The standard assessment tool for neurodevelopment in children aged 1–42 months is the Bayley Scale of Infant Development II (BSID-II).[104] A main component of the BSID-II is the Mental Development Index (MDI), which is a measure of nonverbal cognitive and language development. The MDI is graded on scores of neurodevelopmental delay: >85%, normal; 70%–84%, mild; 55%–69%, moderate; and <55%, severe. A newer version, the Bayley-III, was published in 2006 and has cognitive and language scores but does not use the MDI.[105] The Bayley-III scores tend to be 10 points higher than the BSID-II scores, and some recent studies showed that an MDI <70 correlates with Bayley-III cognitive and language scores <85.[106] In addition, there is some concern that the BSID is not a good assessment of long-term neurodevelopment.[107] These 2 points are important to remember for outcomes presented after the Bayley update, especially in the context of meta-analyses conducted before 2014 (the date of the most recent cutoff data for Bayley-III).

The majority of DHA studies conducted looked at the use of enteral administration of the fat in preterm infants. Recent studies show that administration of supplemental DHA directly

to the infant can help in preventing the drop of DHA levels observed after birth. Baack et al fed preterm infants 50 mg/d of preformed DHA or an MCT control, starting within the first week of birth.[108] Infants receiving the DHA supplement had a significant increase in DHA serum concentrations (2.88–3.55 mol%) as compared with the serum concentrations of the MCT group (2.91–2.87 mol%) by time of discharge or at 38 weeks postmenstrual age. The DHA-supplemented group failed to reach the levels of serum DHA in term infant controls, which were at 4.31 mol%. These values are considerably lower than the DHA levels found in term-born infants in the study by Martin et al discussed earlier.[82] Similar benefit was seen by Collins et al, who gave doses of 40, 80, and 120 mg/kg/d of DHA starting at days 5–6 of life.[109] The increasing dose of DHA led to significant mol% enrichment of DHA in red blood cells to a level near 6% at 28 days in the 80- and 120-mg/kg/d groups. However, this study did not have gestational age–matched term infants for a control group, so near to normal levels can be assumed only on the basis of preexisting data. The interesting results from this study show that even with the high intake of 120 mg/kg/d of DHA, the infants still cannot reach the levels seen in term infants, and there does not appear to be a dose effect from 80–120 mg/kg/d of DHA. A particular concern with this study and many others is that the administration of fat is too late after birth. If DHA levels are decreased by the end of the first week of birth, then supplementation given at the end of the week would have to not only meet the needs but overcome the deficit that has already occurred.

A number of studies have looked at the effect of DHA enteral supplementation on neurodevelopment outcomes.[110-123] A 2011 Cochrane database meta-analysis failed to show a positive effect from DHA at 18 and 24 months on cognitive function as compared with standard enteral formulas.[124] This meta-analysis had limited power, with only 2 studies in the 18-month analysis and 1 study in the 24-month analysis. A larger meta-analysis with mixed analysis for term and preterm infants also did not show a difference in MDI or psychomotor development index scores with DHA supplementation.[125] When the data were stratified to only preterm infants, there was a strong but nonsignificant trend ($P = .06$) for a positive effect for DHA supplementation. The DINO study has been one of the largest (n = 657) multicenter RCTs to examine neurodevelopment with enteral DHA supplementation in VLBW infants.[119] Preterm infants overall receiving the high DHA supplement (1% total fatty acids) compared with standard DHA (0.3% total fatty acids) had a significant reduction in MDI scores <70 ($P = .03$). Stratified by body weight, infants <1250 g saw a significant benefit in mild metal delay (MDI <85, $P = .02$) but no benefit in significant mental delay incidence (MDI <70, $P = .17$). When stratified by sex, girls benefited from DHA supplementation across all MDI scores (MDI <85, $P = .01$; MDI <70, $P = .02$), whereas boys did not benefit from DHA treatment in either MDI group (MDI <85, $P = .94$; MDI <70, $P = .47$). A follow-up of this study was conducted in 2015.[115] No differences were seen in IQ at 7 years of age between children who had received the DHA supplement or no DHA as preterm infants. Stratification by birth weight and sex also failed to show significant differences.

SOFE administration does not effectively maintain DHA levels. ELBW infants who receive SOFE for >28 days can have a 50% reduction of red blood cell DHA concentrations from birth.[126] This reduction can be partially rescued with the administration of enteral formulation (breast milk or formula) prior to reaching 28 days. Administration of MOFE does not prevent a progressive drop in DHA levels, independent of the time at which the PN feeds have been started.[28] However, it does appear that MOFE can prevent as large an initial drop in DHA levels if initiated early, as compared with SOFE feedings. This drop in DHA has been seen in IVFEs supplemented with fish oil as well.[83,127] It may be necessary to consider more aggressive PN feeding strategies within the first day of birth to prevent the initial drop in DHA levels. Once the drop occurs, current PN DHA feeding strategies are inadequate.

No published studies have looked at the effect of new-generation IVFEs containing DHA on neurodevelopmental outcomes. As mentioned, the DHA concentration in preterm infants is sustained at higher levels in fish oil–supplemented PN compared with soy-based emulsions. Yet, these levels fall below DHA concentrations in term infants. It is not clear to what extent a marginal increase in DHA levels would have on overall neurodevelopment. On the basis of studies involving enteral DHA supplementation, it is possible that PN results will show minimal benefit unless DHA levels can be brought significantly higher.

Failure to achieve appropriate growth affects the neurodevelopment of preterm infants. A large cohort study by Ehrenkranz et al of 695 ELBW infants examined the effect of growth on BSID-II MDI scores at 18–22 months of age.[92] The infants were stratified into quartiles for mean weight gain, and the lowest quartile had the lowest mean MDI scores and the largest number of scores that fell <70. The study showed an even stronger association with smaller head circumference growth and MDI scores <70. Head growth and impaired developmental outcomes have been observed in VLBW infants as well.[128] Consistent with this result, a study by Stephens et al regarding the MDI score of ELBW infants at 18 months found that infants with higher energy or protein intake per kilogram of body weight in the first week of life had higher MDI scores.[94] There have not been many positive results to suggest that administration of mixed-fat emulsion is of any benefit to improving weight gain when compared with SOFE alone.[28,31,77,129-131] One study by Vlaardingerbroek et al did find that the administration of MOFE led to greater weight gain in infants at the time of discharge.[29] However, in this study, most infants were on full enteral feeds by day 14, and their dates until discharge were 87 and 95 days for MOFE and SOFE groups, respectively. These results suggest that the infants receiving the MOFE were healthier overall as compared with

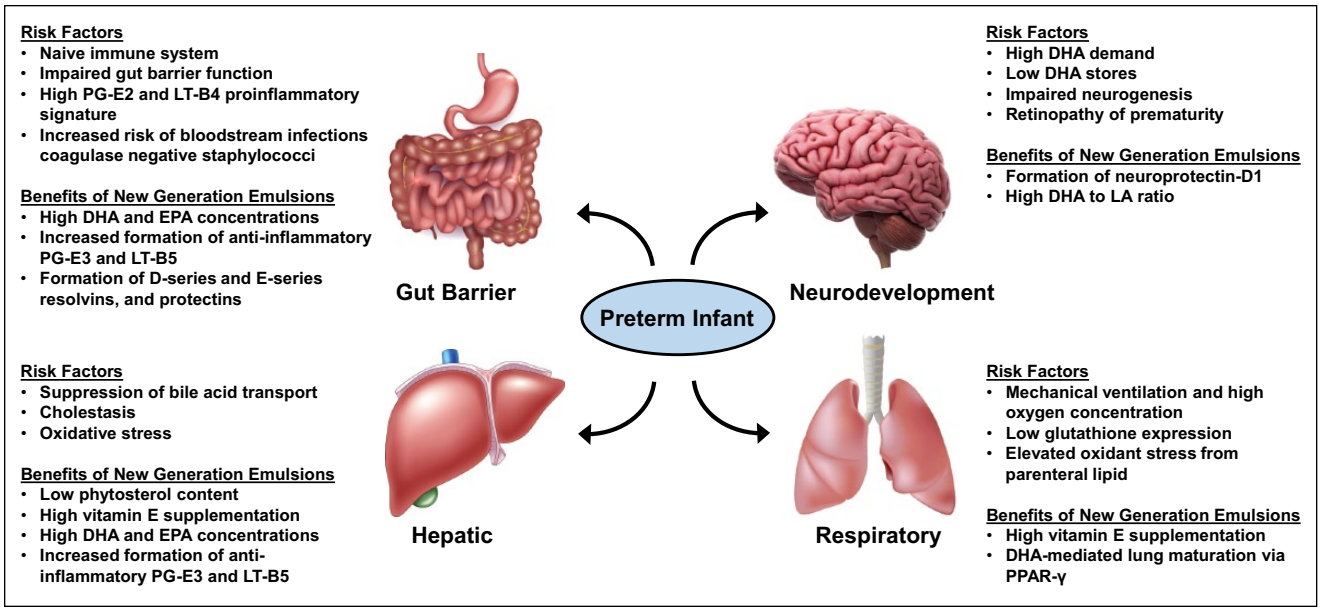

Figure 1. Risk factors from prematurity and current-generation fat emulsions and the potential benefits of new-generation fat emulsions in organ systems. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; LT, leukotriene; PG, prostaglandins; PPAR, peroxisome proliferator-activated receptor. Images © guniita (gastrointestinal tract), Eraxion (brain), tigatelu (liver), alila (lungs) / 123RF.com.

the SOFE infants; regardless, the weight gain did not occur during MOFE administration.

Conclusion

There are several morbidities currently associated with current-generation IVFE administration that could theoretically benefit from the modified compositions of new generation fat emulsions (Figure 1). However, the current evidence does not strongly support the use of new-generation IVFE with regard to decreasing these common morbidities associated with PN. Despite the current evidence, there is far too much variation among treatment protocols to dismiss the potential benefit of n-3 PUFA–enriched IVFEs. Variation in the start of fat treatments, the overall concentration of fat administered, and the rate at which fat is increased to full dose of 3 g/kg/d all affect study outcomes and greatly contribute to the large variation in study results. What can be determined from the majority of research is that meeting the n-3 PUFA needs for the preterm infant is still a large hurdle that needs to be overcome to optimize outcomes in this population. The implementation of standardized protocols across study groups and larger multicenter RCTs are necessary to reach concrete conclusions on the benefit of IVFEs containing fish oil. The use of preclinical models could also benefit our understanding of IVFE in this population.

Understanding the impact of different parenteral fat emulsions on the growth, metabolic function, and developmental outcomes in neonates requires not only well-controlled clinical studies but preclinical studies in appropriate animal models. Various models have been used to study IVFE, including the mouse, guinea pig, and domestic pig, but only the domestic pig has been able to reproduce the condition of prematurity in the neonatal stage of postnatal life. Further studies in IVFE administration in these models, with a focus on the administration of DHA, could help facilitate a better understanding of the obligate needs of preterms and how best to meet these needs.

Statement of Authorship

All authors equally contributed to the conception, design, and drafting of the manuscript; critically revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Role of Vitamin D in Inflammatory Bowel Disease

Berkeley N. Limketkai, MD[1,2]; Gerard E. Mullin, MD, CNSP[2]; David Limsui, MD[1]; and Alyssa M. Parian, MD[2]

Abstract

Vitamin D is a secosteroid hormone that possesses immunomodulatory properties and has been demonstrated to potentially influence inflammatory bowel disease (IBD) pathogenesis and activity. Epidemiologic data have associated vitamin D deficiency with an increased risk of IBD, hospitalizations, surgery, and loss of response to biologic therapy. Conversely, IBD itself can lead to vitamin D deficiency. This bidirectional relationship between vitamin D and IBD suggests the need for monitoring and repletion of vitamin D, as needed, in the IBD patient. This review discusses the role of vitamin D in IBD and provides practical guidance on vitamin D repletion. (*Nutr Clin Pract*. 2017;32:337-345)

Keywords

cholecalciferol; Crohn's disease; ergocalciferol; inflammatory bowel diseases; ulcerative colitis; vitamin D; vitamin D deficiency

Inflammatory bowel disease (IBD)—primarily comprising Crohn's disease (CD) and ulcerative colitis (UC)—is characterized by chronic inflammation in the gastrointestinal tract. The underlying causes of IBD are yet unclear, although the current paradigm of pathogenesis involves the interaction between genetic and environmental risk factors.

Early population-based studies suggested a genetic determinant of disease when first-degree relatives of patients with IBD were found to possess an increased risk of developing CD or UC.[1-3] However, the risk conveyed by identified genetic mutations was small and inconsistent across populations.[4-7] Moreover, discordance in monozygotic twin studies indicated that nonheritable factors strongly contributed to IBD pathogenesis (Figure 1).[2,3] Several epidemiologic studies later suggested several potential environmental risk factors for incident IBD, such as gastrointestinal infections, antibiotic use, oral contraceptives, and nutrition.[8-11]

Vitamin D had traditionally been solely implicated in calcium and phosphorus homeostasis, although it was more recently found to possess immunomodulatory properties. Meanwhile, emerging epidemiologic evidence demonstrated a north-south gradient of IBD, where more northern regions (with less sunlight exposure and natural vitamin D synthesis) had a greater incidence of IBD than southern regions (with more sunlight exposure).[12-14] These findings prompted further investigation into the role of vitamin D in IBD pathogenesis and disease modification. Conversely, IBD can itself lead to vitamin D deficiency through reduced dietary consumption, decreased physical activity with sunlight exposure, and malabsorption of fat-soluble vitamins. In this review, we discuss these bidirectional effects of vitamin D status and IBD, based on a representative but nonexhaustive summary of the existing literature. We also address practical aspects of vitamin D repletion for IBD in the current absence of clear guidelines.

Vitamin D

Vitamin D belongs to a family of fat-soluble secosteroid hormones and comprises 2 major forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). In humans, vitamin D can be accumulated through dietary sources or synthesized de novo from sterol precursors. Since ergosterol, the precursor of vitamin D_2, is typically found in yeast and fungi (ergot), humans accumulate ergocalciferol through consumption of water plants, fish that feed on phytoplankton, fortified foods, or dietary supplements.[15,16] For cholecalciferol, ultraviolet B exposure (280–315 nm) in the epidermis leads to conversion of 7-dehydrocholesterol (7-DHC) to pre–vitamin D_3, which subsequently undergoes rapid thermal isomerization to vitamin D_3.[17,18] Photoconversion of 7-DHC to pre–vitamin D_3 can reach a maximum concentration within 15 minutes of

From the [1]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, California, USA; and the [2]Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

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Corresponding Author:
Berkeley N. Limketkai, MD, Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 300 Pasteur Drive, Alway 211, Palo Alto, CA 94305, USA.
Email: berkeley.limketkai@gmail.com

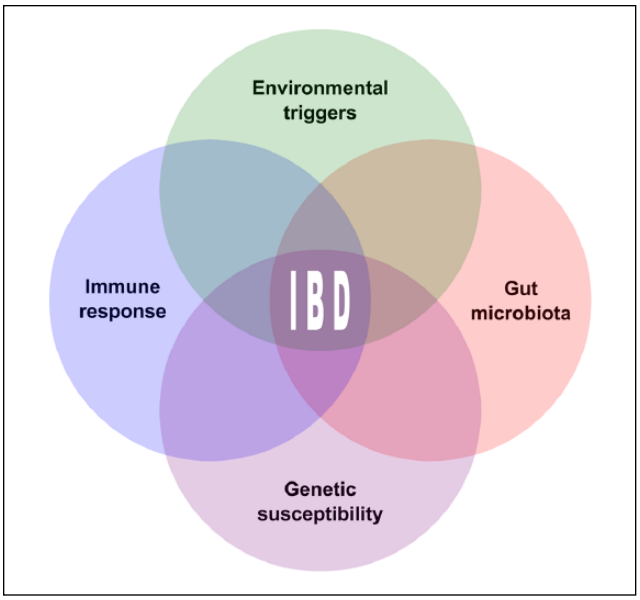

Figure 1. The current paradigm of inflammatory bowel disease (IBD) pathogenesis involves the interaction among an individual's genetic risk, gut microbiota, environmental factors, and an aberrant host immune response.

ultraviolet B exposure.[19] In the case of prolonged sunlight exposure, excess 7-DHC is shunted to biologically inactive photoisomers: tachysterol and lumisterol. Excess previtamin D_3 and vitamin D_3 in the epidermis can also undergo photodegradation, so prolonged sunlight exposure does not lead to vitamin D toxicity.[20]

Due to its hydrophobic nature, vitamin D circulates in the bloodstream while bound to the vitamin D binding protein and, to a lesser degree, albumin.[21,22] Vitamin D is first hydroxylated in the liver by the mitochondrial (CYP27A1) and microsomal (CYP2R1) cytochrome P450 isoforms to form 25-hydroxyvitamin D (25[OH]D) before being converted in the renal tubules by CYP27B1 to its active metabolite: 1,25-dihydroxyvitamin D ($1,25[OH]_2D$; Figure 2).[23-25]

Vitamin D exerts its biologic effect through the classical activation of transcription and through more rapid-acting membrane-bound receptors. The active metabolite $1,2(OH)_2D$ initially binds the vitamin D receptor (VDR).[26] VDR is a member of the steroid receptor superfamily of ligand-activated transcription factors, where once activated, it translocates into the nucleus to form a heterodimer with the retinoid X receptor.[27] The VDR–retinoid X receptor complex then recruits several coactivator proteins, selectively binds the vitamin D response element, and facilitates RNA polymerase II–mediated transcription of respective target genes.[28-30] Alternatively, the $1,25(OH)_2D$ hormone is able to generate more rapid extragenomic effects through interaction with membrane-bound VDR and/or membrane-associated rapid-response steroid-binding receptors.[31,32]

Vitamin D and the Immune System

Although vitamin D has traditionally been known for its prominent role in calcium and phosphorus homeostasis, emerging data have shown it to instead possess multiple effects.[16] In particular, studies in the 1980s began to implicate vitamin D in immune function. The discovery that $1,25(OH)_2D$ induced the differentiation of murine myeloid leukemia cells to macrophages prompted a search for its receptor in these cells.[33] VDR was subsequently found in a broad host of immunologic cells, with constitutive expression in diverse hematopoietic cells, including myeloblasts, promyelocytes, monoblasts, and macrophages.[34-36] Although resting T lymphocytes have negligible VDR levels, VDR expression is inducible by T-cell activation.[35,37]

Evidence of 25(OH)D-1-α-hydroxylase (CYP27B1) in macrophages, dendritic cells, and B cells[38-40] further suggested involvement of vitamin D in the regulation of the immune system. That is, local conversion of 25(OH)D to the active $1,25(OH)_2D$ represents an autocrine or paracrine mechanism of immune cell signaling. Furthermore, expression of 1-α-hydroxylase in these cells is synergistically induced by interferon γ and Toll-like receptor (TLR) activation,[41,42] which are often associated with immune system function. This mechanism of induction differs from the role of renal 1-α-hydroxylase in calcium homeostasis, which is regulated by the parathyroid hormone and $1,25(OH)_2D$.

Of interest in IBD, vitamin D possesses inhibitory effects on immunity. In monocytes, $1,25(OH)_2D$ can suppress TLR2 and TLR4 expression, whereby use of lipopolysaccharide or lipoteichoic acid on affected cells would fail to stimulate tumor necrosis factor α (TNF-α) production.[43] In lymphocytes, vitamin D's modulatory effects occur through several putative mechanisms. First, vitamin D impairs lymphocyte proliferation and differentiation.[40,44-46] It further inhibits differentiation and maturation of dendritic cells,[47-49] which indirectly leads to T-cell anergy by impaired activation of alloreactive T cells.[49,50] Second, vitamin D exerts an immunomodulatory effect by expansion of regulatory T cells.[51-54] In trinitrobenzene sulfonic acid–treated mice used to produce colitis, exogenous $1,25(OH)_2D$ administration shifts the T helper 1 (Th1) / Th17 profile to Th2 and regulatory T cells.[55] Third, vitamin D modulates the release of inflammatory cytokines. Vitamin D favors the synthesis of anti-inflammatory cytokines over proinflammatory cytokines.[43,45,55-61]

Vitamin D is additionally involved in innate immunity through induced expression of pattern recognition receptors and antimicrobial peptides. In a state of epidermal injury, $1,25(OH)_2D$ stimulates transcription of genes for TLR2 and its coreceptor CD14 in keratinocytes.[62] TLRs belong to a family of molecular pattern recognition receptors that sense microbial components and signal downstream expression of antimicrobial peptides. TLR activation in macrophages induces expression of VDR, CYP27B1, and cathelicidin.[42] Moreover, the $1,25(OH)_2D$ pathway directly activates transcription of human

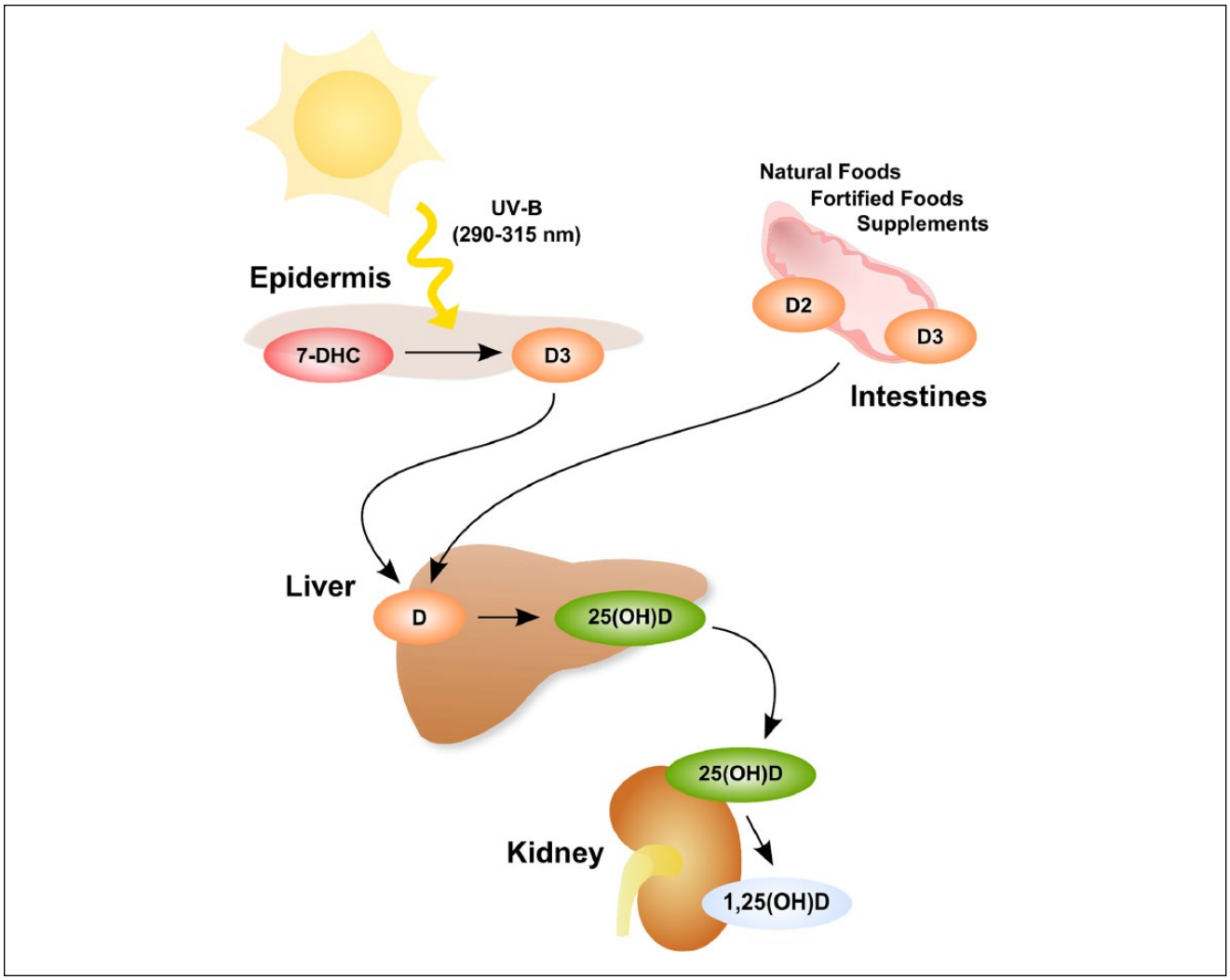

Figure 2. Vitamin D synthesis and metabolism. Vitamin D can be synthesized (ultraviolet-mediated conversion of 7-dehydrocholesterol [7-DHC] to cholecalciferol) or consumed from food sources. Vitamin D is then hydroxylated in the liver to 25-hydroxyvitamin D and in the renal tubules to 1,25-dihydroxyvitamin D (active form). UV-B, ultraviolet B.

cathelicidin antimicrobial peptide (CAMP) and defensin β_2 (DEFB2/HBD2).[63,64] Inversely, a defect or deficiency in VDR, CYP27B1, or $1,25(OH)_2D$ can impair induced expression of cathelicidin.[42,62]

Vitamin D and Effects on IBD

Effects on IBD Pathogenesis

The underlying pathologic mechanisms of IBD involve dysregulation of cell-mediated immunity in the context of interactions between genetic and environmental factors (Figure 1). Given vitamin D's influence on immune function, causal associations between vitamin D and IBD have been investigated.

Murine studies have demonstrated a biologic relationship between vitamin D and the development of colitis. As with murine models of IBD and in humans with this disease, gastrointestinal mucosal inflammation is accompanied by increases in proinflammatory cytokines (eg, interleukin 2 [IL-2], IL-12, interferon γ, TNF-α).[65-67] However, IL-10 downregulates the Th1/Th17 cellular responses. IL-10 knockout germ-free mice permit luminal antigens to elicit a proinflammatory response due to lack of counterregulatory protective mechanisms.[68] In the IL-10 knockout mice, concurrent VDR knockout leads to severe and accelerated IBD.[65,69,70] Similarly, vitamin D–deficient mice often manifest diarrhea, wasting disease, and subsequent death, while vitamin D–sufficient mice may not develop any IBD symptoms.[71] Administration of exogenous vitamin D or a VDR agonist in IBD mouse models has been shown to reduce TNF-α and suppress colitis.[55,71-74]

Epidemiologic studies have additionally correlated vitamin D with IBD pathogenesis in humans. Northern regions, where

Table 1. Vitamin D Interventions and Inflammatory Bowel Disease (IBD) Activity.

Reference	IBD Type	Cohort Size, n	Interventions	Outcomes
Jorgensen et al (2010)[91]	Crohn's disease in remission	94	1200 IU/d vs placebo	• Increased vitamin D levels • Similar relapse rate (13% vs 29%, $P = .06$)
Yang et al (2013)[90]	Crohn's disease (mild to moderate)	18	1000 IU/d with incremental escalation of dosing per week, up to 5000 IU/d, based on serum 25(OH)D levels	• Increased vitamin D levels • Improved quality of life • Decreased CDAI • No change in inflammatory markers
Pappa et al (2014)[122]	Crohn's disease and ulcerative colitis	63	1000 IU/d (summer/fall) or 2000 IU/d (winter/spring) vs 400 IU/d	• Lower CRP and interleukin 6
Raftery et al (2015)[123]	Crohn's disease in remission	27	2000 IU/d vs placebo	• Increased vitamin D levels • Maintenance of intestinal permeability • Improved quality of life • Lower CRP • Similar CDAI

CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein.

sunlight exposure and natural vitamin D synthesis are lower, have a higher incidence of IBD.[12-14] The European Collaborative Study on Inflammatory Bowel Disease specifically evaluated the north-south gradient by comparing incidence rates between northern and southern European centers.[13] The study of 2201 patients revealed 80% greater rates of CD and 40% greater rates of UC in the north. Subsequent studies showed similar geographic variations in France[12,75-77] and Scotland.[78]

Analysis of prospectively collected data from the Nurses' Health Study found that higher predicted vitamin D levels were associated with a lower risk of developing CD but not UC.[79] In women with the highest intake of oral vitamin D (via diet and supplements), there was a significantly lower risk of developing UC. These findings suggest that the effect of vitamin D on CD pathogenesis may be stronger than on UC pathogenesis, which would be consistent with $1,25(OH)_2D$ being known to down-regulate Th1 cells (postulated mediator of CD) more than Th2 cells (postulated mediator of UC). Nonetheless, a key limitation of the study was the lack of measured serum vitamin D levels while instead relying on predicted levels based on dietary and supplement intake, sunlight exposure, race, and body mass index. There is yet no direct evidence that links vitamin D deficiency to an increased risk of IBD, although the preliminary data supporting this relationship are compelling.

Effects on Clinical Outcomes

In addition to possibly contributing to IBD pathogenesis, vitamin D may influence the clinical course of IBD. Vitamin D levels are lowest at the end of winter and correspond to the most common time for patients to experience flares.[80-83] In a nationwide study of hospitalizations throughout the United States, low sunlight exposure was similarly found to be associated with increased hospitalizations, length of stay, and bowel surgery among patients with IBD.[84] A large retrospective cohort of 3217 patients with IBD in Massachusetts also found vitamin D deficiency to be an independent risk factor for hospitalizations and surgery.[85] Treatment to normalize vitamin D levels was associated with a lower risk of subsequent surgery in CD (odds ratio, 0.56; 95% confidence interval [95% CI], 0.32–0.98) but not UC. Patients with CD who normalized their serum vitamin D levels also had a significantly lower C-reactive protein (CRP), although this effect was not found among UC patients.

Vitamin D deficiency has also been associated with increased IBD activity scores and lower quality of life scores. In a retrospective study of 504 patients with IBD (403 CD, 101 UC), patients with vitamin D levels <20 ng/dL had significantly greater odds of having a ≥3-point increase on the Harvey-Bradshaw Index or Ulcerative Colitis Disease Activity Index (odds ratio, 1.77; $P = .005$).[86] Moreover, among those with vitamin D deficiency, mean Short Inflammatory Bowel Disease Questionnaire scores were significantly lower (–3.3; $P = .002$), a reflection of worse quality of life. In a cross-sectional study of 34 UC patients, vitamin D–deficient patients were more likely to have increased disease activity based on the 6-point Partial Mayo Index (68% vs 33%; $P = .04$); they were also more likely to need treatment with corticosteroids (47% vs 7%; $P = .02$).[87]

To date, randomized trials of vitamin D administration in patients with IBD have predominantly evaluated bone mineral density as the primary outcome,[88,89] with a dearth of similar studies specifically evaluating IBD severity (Table 1). A small open-label trial of 18 patients with CD treated with vitamin D_3 supplementation, titrated to a target of 40 ng/mL of 25(OH)D, found improvement in Crohn's Disease Activity Index (CDAI) and quality-of-life measures but no change in inflammatory markers.[90] A larger Danish trial randomized 94 patients with CD in remission to receive 1200 IU of vitamin D_3 or placebo

daily for 12 months with a primary endpoint of clinical relapse.[91] Vitamin D supplementation was shown to reduce the relapse rate from 29% to 13%. The change was nonsignificant ($P = .06$) but may reflect inadequate power. Another trial included 37 inactive patients with CD randomized to 25(OH)D or $1,25(OH)_2D$ with CDAI, quality-of-life scores, and CRP levels as secondary outcomes.[92] The group that received $1,25(OH)_2D$ experienced a significant decline in CDAI, Short Inflammatory Bowel Disease Questionnaire, and CRP by week 6, which was not observed in the 25(OH)D group. There was no difference between the groups by 12 months, although the change from baseline was not reported. The study was nonetheless limited by a small sample size and lack of comparison to placebo.

Effects on IBD Treatment

Vitamin D has been shown to downregulate powerful proinflammatory cytokines, such as TNF, which prompted investigation into the effects of vitamin D on anti-TNF therapy. A retrospective study of 101 patients with IBD found that those with vitamin D insufficiency had earlier cessation of anti-TNF therapy (hazard ratio, 2.13; 95% CI, 1.03–4.39), especially among those not taking vitamin D supplementation (hazard ratio, 3.40; 95% CI, 1.14–10.19).[93]

In a prospective study of 68 patients with IBD (56 CD, 12 UC) starting anti-TNF therapy, extreme vitamin D deficiency (<4 ng/mL) was independently associated with pretreatment antinuclear antibody positivity.[94] Pretreatment antinuclear antibody positivity was in turn associated with failure of the first anti-TNF throughout the mean follow-up time of 4 years. As >90% of the patients had levels <20 ng/mL, the study was not adequately powered to evaluate the relationship between vitamin D deficiency and anti-TNF failures, although none of the patients with vitamin D levels >20 ng/mL required switching anti-TNF medications or surgical intervention. The study authors concluded that vitamin D monitoring should start at diagnosis and repletion should be aggressive to prevent development of autoantibodies that can lead to anti-TNF therapy failures.

IBD and Effects on Vitamin D

The relationship between vitamin D deficiency and IBD may be bidirectional. While vitamin D deficiency may influence IBD pathogenesis and severity, the converse is also true. Patients with IBD possess an increased risk of vitamin D deficiency due to relative lack of sunlight exposure from avoidance (especially in the setting of thiopurine use) or decreased physical/outdoor activity (in the setting of illness), decreased fortified dairy intake from intolerance, increased metabolic demand, and increased excretion into the stool.[16,95] Moreover, illness and inflammation may themselves contribute to low vitamin D levels. A recent systematic review of 290 prospective cohort studies and 172 randomized trials associated chronic illness with lower vitamin D levels and generally did not observe an improvement in disease outcomes with vitamin D supplementation.[96] In CD, vitamin D malabsorption can occur due to small bowel inflammation, even with quiescent CD.[97] Indirectly, individuals with terminal ileal inflammation or prior resection may have relative bile insufficiency with compromised absorption of fat-soluble vitamins, which includes vitamin D.[98,99] Medications commonly used by patients with IBD may also interfere with vitamin D absorption and metabolism. For one, corticosteroids have been shown to reduce calcium absorption and impair vitamin D metabolism.[100-102] Cholestyramine can decrease the absorption of vitamin D and other fat-soluble vitamins.[103]

Given the influence of IBD and related factors on vitamin D levels, one must always consider reverse causation when interpreting studies that associate IBD severity with low vitamin D. That is, does vitamin D deficiency aggravate IBD or does IBD lead to vitamin D deficiency? Or is there a third, unrecognized factor influencing both?

Vitamin D Repletion

Vitamin D status is best evaluated by serum 25(OH)D measurement, with levels >30 ng/mL generally considered "normal," 20–30 ng/mL "insufficient," and <20 ng/mL "deficient."[16] However, there is no consensus on the optimal vitamin D level for the general population, let alone the IBD population. The absorption of calcium, magnesium, and phosphate is maximized at serum vitamin D levels >33 ng/mL,[104] although higher levels may be required for its immunomodulatory effects. One study found that patients with IBD with serum vitamin D levels between 50–59 ng/mL had the highest quality-of-life scores.[105]

There are several oral preparations of vitamin D: ergocalciferol (D_2), cholecalciferol (D_3), and calcitriol ($1,25[OH]_2D$). The use of calcitriol is limited by its high risk for hypercalcemia. In the past, ergocalciferol was thought to be as effective as cholecalciferol and more convenient, since it can be given at higher doses less frequently. However, more recent studies have shown cholecalciferol to be more effective at increasing and maintaining serum 25(OH)D levels. Two studies of healthy volunteers found that D_3 has a longer duration of action and resulted in a 2- to 3-fold greater increase in vitamin D levels than D_2.[106,107] A pediatric IBD study found that 2000 IU of vitamin D_3 daily increased serum 25(OH)D levels significantly more than 2000 IU of vitamin D_2 daily.[108] Moreover, patients with CD in remission had a 30% reduction in the ability to absorb vitamin D_2.[97] However, a separate study of vitamin D_3 supplementation did not detect a difference in absorption between patients with CD and healthy controls.[109]

The Institute of Medicine currently recommends a daily intake of 600 IU/d of vitamin D_3 for all persons ≤70 years old and 800 IU/d for persons >70 years old, with a maximum of 4000 IU/d.[110] By contrast, the Endocrine Society recommends 1500–2000 IU/d of vitamin D_3, with a maximum of 10,000

IU/d.[111] There are no official dose recommendations for patients with IBD, but it is important to note that patients with CD in remission may already have a 30% lower absorption of vitamin D than that of the general population.[97] A small study of 18 patients with CD with vitamin D deficiency found that doses of cholecalciferol as high as 5000 IU were required to achieve a serum vitamin D level ≥40 ng/mL over a 24-week period.[90] One study recommended that the dose of cholecalciferol in patients with IBD be calculated based on the degree of deficiency. Patients with vitamin D levels of <4, 4–10, 10–16, 16–24, and 24–30 ng/mL should receive 5000, 4000, 3000, 2000, and 1000 IU/d, respectively. Serum levels should be rechecked at 3 months and vitamin D dose adjusted at that time.[112] Current smokers and obese patients are more prone to vitamin D deficiency and typically require higher dosing to reach adequate levels.[111]

Sunlight exposure of the face, arms, and hands in those with fair, beige, or cream-colored skin for 5 minutes 2 to 3 times a week during a July noon in Boston is adequate for vitamin D intake. Although excessive sun exposure does not result in vitamin D toxicity, prolonged exposure carries other health risks.[16,113] Multiple studies have shown that high doses of oral vitamin D supplementation (even up to 10,000 IU/d) are well tolerated without evidence of hypercalcemia.[114-118] Serum vitamin D levels consistently above 200 ng/mL are considered potentially toxic.[119] Vitamin D toxicity manifests as hypercalcemia, which can lead to vascular and tissue calcification affecting the heart, blood vessels, and kidneys; vitamin K_2 used in conjunction with vitamin D may improve calcium homeostasis and reduce the risk of arterial calcification.[120] The effect of calcium on mortality is nonetheless unclear. In a recently published analysis of the Cancer Prevention Study II Nutrition Cohort, with 132,823 participants, supplemental calcium intake was associated with lower mortality in women and higher mortality in men.[121]

Conclusion

Vitamin D appears to play an important role in IBD. On one hand, a constellation of animal, in vitro, and epidemiologic data suggest that vitamin D exerts effects on IBD pathogenesis and disease activity. Emerging data have additionally associated vitamin D status with the durability of biologic therapy. On the other, the presence of IBD itself can lead to vitamin D deficiency. There is additionally the distinct possibility that unmeasured confounders may influence both vitamin D levels and IBD activity. These opposing phenomena complicate the interpretation of studies that have associated vitamin D deficiency with IBD activity, as the presence and direction of causality may be challenging to clarify, especially since bidirectionality may not be the explanation for the observed associations. That is, did the low vitamin D levels lead to worse IBD activity, or vice versa? In any case, more research is needed to clarify the associations between vitamin D and IBD while investigating the clinical importance of checking, correcting, and monitoring vitamin D levels to improve overall clinical outcomes.

Statement of Authorship

B. N. Limketkai, G. E. Mullin, D. Limsui, and A. M. Parian participated in the conception of the review, the drafting of the manuscript, and the critical revision. All authors have given final approval, and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Review

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Vitamin A Supplementation for the Prevention of Bronchopulmonary Dysplasia in Preterm Infants: An Update

Emily Schwartz, MS, RD, CSP, CNSC[1]; Rena Zelig, DCN, RDN, CDE, CSG[2]; Anna Parker, DCN, RD, CDE[2]; and Stephani Johnson, MS, RD[2]

Abstract

Bronchopulmonary dysplasia (BPD) is a common complication of premature birth and is associated with significant morbidity. Vitamin A supplementation has been suggested as a potential preventative measure against BPD due to its role in lung maturation and because preterm infants are particularly predisposed to vitamin A deficiency. The aim of this review was to determine whether vitamin A supplementation reduces BPD risk among preterm infants. PubMed, CINAHL, and Web of Science databases were searched with the keywords "bronchopulmonary dysplasia," "vitamin A," and "preterm infants" and with the time frame of 2006–2016, and 4 studies were selected for review per the inclusion criteria. Only 1 study found a significant reduction in BPD risk associated with vitamin A supplementation; however, 2 studies indicated a nonsignificant benefit and may have been underpowered to show statistical significance. One study revealed an increased risk of sepsis associated with vitamin A supplementation (for infants weighing >1000 g at birth), but no risk was seen with vitamin A supplementation in the other studies. Because intramuscular vitamin A has shown benefit with minimal risk, continued supplementation for preterm infants is warranted. Future studies aimed at assessing infant groups that are most likely to benefit from supplementation (based on birth weight or other conditions), as well as determining the optimal dosing while minimizing injections, would be beneficial. (*Nutr Clin Pract*. 2017;32:346-353)

Keywords

premature infant; low birth weight; vitamin A; bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a common complication of premature birth. BPD affects approximately 20% of very low birth weight infants and >50% of extremely low birth weight (ELBW) infants, and it can result in significant morbidity.[1,2] Despite advances in respiratory care, BPD prevalence has not dramatically changed in the past 30 years.[3] Although mortality associated with BPD has dropped in recent years (contributing to only 0.2% of cardiopulmonary-related deaths for all children <1 year old), BPD remains a major cause of death for premature infants.[4] BPD has also been associated with growth failure, developmental delays, cerebral palsy, increased neonatal intensive care unit (NICU) stay, and an increased likelihood for requiring medications and/or supplemental oxygen after discharge.[1,4,5]

In 1967, Northway et al originally defined BPD as "a new chronic pulmonary syndrome associated with the use of intermittent positive pressure respirators (IPPR) and high oxygen for longer than 150 hours (6 days)."[6] However, with the advent of gentle ventilation with antenatal corticosteroids and surfactant treatment, the clinical definition of BPD has evolved over time to include additional respiratory parameters.[7] In 2000, a consensus of workshop participants from the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute proposed a severity-based definition of BPD, later validated in the literature.[8,9] These criteria are shown in Table 1.

The interruption in lung development characteristic of preterm infants may disrupt the development of the alveoli and microvasculature within the peripheral lung, resulting in low numbers of alveoli for infants with BPD.[10] Animal models indicate that BPD is also characterized by pulmonary inflammation and thicker air-blood barriers for gas exchange, though it is currently unclear whether these manifestations are caused by lifesaving measures performed at birth or by preterm birth itself.[10-12] Pulmonary fibrosis is also seen in BPD, although the precise mechanism is still under debate and more recent postmortem examinations following surfactant treatment have

From [1]Providence Park Hospital, Novi, Michigan, USA; and [2]Rutgers School of Health Professions, Newark, New Jersey, USA.

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Corresponding Author:
Emily Schwartz, MS, RD, CSP, CNSC, 24425 Farmington Road, Farmington Hills, MI 48336, USA.
Email: emilyschwartzrd@gmail.com

Table 1. National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute Severity-Based Diagnostic Criteria for Bronchopulmonary Dysplasia.[8,9]

	Gestational Age	
Criteria	<32 wk	≥32 wk
Oxygen therapy	O_2 >21% for at least 28 d	O_2 >21% for at least 28 d
Severity		
Time point of assessment	36-wk postmenstrual age[a] or discharge home (whichever comes first)	56 d postnatal age[b] or discharge home (whichever comes first)
Mild	Breathing room air	Breathing room air
Moderate	Need for <30% O_2	Need for <30% O_2
Severe	Need for >30% O_2 and/or positive pressure (PPV or nasal CPAP)	Need for >30% O_2 and/or positive pressure (PPV or nasal CPAP)

CPAP, continuous positive airway pressure; O_2, oxygen; PPV, positive pressure ventilation.
[a]Gestational age.
[b]Age since birth.

shown less significant fibrosis.[4] Generally, risk factors for the development of BPD include premature birth, low birth weight (with risk increasing inversely with birth weight), respiratory failure, oxygen toxicity, mechanical ventilation (especially positive pressure resulting in lung overdistention), infections (antenatal, postnatal, and maternal—particularly perinatal adenovirus, cytomegalovirus, and maternal chorioamnionitis), pulmonary vascular damage, pulmonary inflammation, and/or pulmonary edema as a consequence of patent ductus arteriosus or fluid overload.[4,13] BPD prolongs infants' need for mechanical ventilation and/or supplemental oxygen, increases airway reactivity (resulting in bronchospasm) and airway resistance, decreases lung compliance, and triggers pulmonary hypertension.[4] Pulmonary symptoms and complications can persist into adulthood, and cardiovascular function may also be affected.[4]

Management strategies for BPD exist to target prevention and treatment. Prevention tactics include

- prevention of prematurity,
- prenatal glucocorticoid administration for those at risk of preterm delivery,
- exogenous surfactant replacement,
- ductus arteriosus closure,
- avoidance of excessive fluid administration,
- treatment of infection,
- adequate nutritional provision,
- antioxidant therapy (including copper-zinc superoxide dismutase and vitamin A), and
- ventilator management (though the most appropriate management strategy is still under debate).[4]

Treatment options are typically aimed at symptom management and include supplemental oxygen, diuretics, anti-inflammatories/bronchodilators, mucolytics, adequate nutrition/protein intake, and glucocorticoids.

Vitamin A and Preterm Infants

Vitamin A is the collective term for a group of fat-soluble retinoids that include retinol, retinal, and retinyl esters.[14] In all forms, vitamin A is absorbed by duodenal mucosal cells after solubilizing into micelles in the lumen of the intestine.[14] Retinyl esters are converted first to retinol, then to retinal, and finally to retinoic acids; the majority of the body's vitamin A stores are converted back to retinyl esters for hepatic storage, though vitamin A may also be stored in the eye and lung.[14] Plasma retinol levels are typically measured to assess vitamin A status, but this practice has limitations: hepatic vitamin A stores are depleted before plasma levels are affected; thus, marginal vitamin A deficiency may not be evident by plasma measurements alone.[14] Dose-response tests are occasionally used in which small amounts of vitamin A are administered and changes in serum levels are assessed, although simple serum levels are considered adequate for assessing significant deficiency in clinical practice.[14]

Preterm infants are at a particularly significant risk for vitamin A deficiency for several reasons. Hepatic vitamin A reserves are limited in preterm infants, as are serum levels of vitamin A and plasma retinol binding protein (responsible for vitamin A transport), because maternal vitamin A is primarily supplied to the fetus during the third trimester.[15] Provision of adequate vitamin A to replace this loss after birth may be challenging. Establishing adequate enteral feedings can be difficult in preterm infants. Even for those infants who can tolerate enteral feedings, vitamin A absorption by the immature gut may be poor.[15,16] Parenteral nutrition is often used with or in place of enteral nutrition; however, significant amounts of parenteral vitamin A may be lost via photodegradation and adsorption to intravenous plastic tubing.[15] Vitamin A may be added to lipid emulsions prior to administration to improve efficacy of delivery.[17] However, intramuscular (IM) vitamin A supplementation is associated with significant improvements in

biochemical vitamin A status and has become the typical route of choice in this population.[18] Although optimal serum vitamin A levels for preterm infants are not known, concentrations <200 μg/L are generally considered deficient, and levels <100 μg/L suggest severe deficiency.[19] Other authors suggest that the ratio of retinol to retinol binding protein is a better indicator of vitamin A status in preterm infants, with a ratio of <0.7 considered suboptimal.[18,20]

Vitamin A and BPD

The role of vitamin A in BPD has been a topic of interest since the 1970s.[21] Vitamin A is involved in the proliferation and maintenance of epithelial cells, including those of the respiratory tract; it is necessary for both cellular differentiation and surfactant production within the lung.[15,22] In addition, it is required for the photosensitive visual pigment within the retina and the development of the reproductive system, and it has antioxidant and immune-modulating properties.[15] In murine models, vitamin A deficiency has been shown to induce negative histologic changes within the respiratory tract, resulting in necrotizing tracheobronchitis and squamous metaplasia, impaired healing, loss of cilia, increased infection risk, and decreased alveoli numbers within the lung parenchyma.[15,23] Supplementation with vitamin A and resolution of deficiency have been shown to reverse many of these changes, as well as preserve alveolarization, which is consistent with changes observed in preterm infants.[5,15,16,24,25]

Earlier studies began establishing a link between vitamin A deficiency and BPD in the 1980s and 1990s. Multiple observational studies found significantly higher rates of vitamin A deficiency among preterm infants who developed BPD as compared with infants who did not develop BPD.[16,26,27] A large multicenter randomized blinded trial (n = 807) published in 1999 on behalf of the NICHD Neonatal Research Network found that 5000 IU of vitamin A supplemented 3 times weekly for 4 weeks significantly reduced biochemical vitamin A deficiency as well as incidence of BPD (then termed *chronic lung disease*) in ELBW infants.[28] In a recent systematic assessment of currently available pharmacologic therapies for BPD prevention, Jensen et al concluded that caffeine and vitamin A are the only therapies found to prevent BPD without major adverse side effects.[29] However, some studies have shown null effects, and the use of vitamin A supplementation for this purpose is still not without controversy.[30] Tolia et al sought to determine whether vitamin A shortages affected BPD incidence and mortality risk, and they found no change in outcomes even when vitamin A was unavailable.[31] Some estimates have indicated that only 20% of neonatal programs routinely supplement vitamin A for preterm infants.[32] One of the primary barriers to use is the concern that the pain inflicted by administering a total of 12 IM shots outweighs the modest short-term benefits shown in the literature.

A Cochrane review published in 2011 reviewed 9 randomized controlled trials investigating the use of vitamin A supplementation for improving outcomes for preterm infants.[19] Results indicated a trend toward reduced supplemental oxygen requirement and mortality with the use of IM vitamin A supplementation. Enteral vitamin A supplementation was utilized in 1 study reviewed, and it showed no benefit for BPD risk.[19,30] However, long-term follow-up data (at 18–22 months corrected age) showed no benefit or harm associated with the use of vitamin A.[19] Since this review was published, additional studies have been done investigating the relationship between vitamin A supplementation and BPD risk, warranting further review. The aim of this review is to determine whether vitamin A supplementation reduces the risk for BPD in preterm infants.

Method

A literature search was completed according to the search strategy described in Table 2. PubMed, CINAHL, and Web of Science databases were searched with the key terms "preterm infants," "vitamin A," and "bronchopulmonary dysplasia," and studies published between 2006 and 2016 were evaluated. Only primary studies were included for review. Studies were included that utilized vitamin A supplementation as an intervention (or retrospectively reviewed vitamin A supplementation for its effect on outcomes) and specifically looked at BPD incidence as an outcome. Four studies (1 randomized controlled trial and 3 cohort studies) met inclusion criteria and are appraised here. A summation of their data is shown in Table 3.

Literature Review

Kiatchoosakun et al published a double-blind randomized controlled trial in 2014 investigating the use of vitamin A supplementation for preventing BPD in preterm very low birth weight infants.[33] Preterm infants (n = 80) with birth weights <1500 g were randomized to receive either 5000 IU of IM vitamin A 3 times weekly for 4 weeks or placebo (in this case, a sham injection procedure was followed to avoid unnecessary pain and side effects for control group subjects while maintaining blinding). Usual practices for enteral/parenteral feedings, mechanical ventilation, and oxygen therapy were followed. Vitamin A supplementation in this study was associated with a significant reduction in ventilator-dependent days ($P = .03$) and length of stay ($P = .002$). Infants receiving vitamin A supplements also experienced a lower BPD incidence ($P = .21$), retinopathy ($P = .07$), nosocomial sepsis ($P = .43$), and necrotizing enterocolitis ($P = .57$), though the results were not statistically significant. The authors concluded that because vitamin A supplementation appeared to significantly reduce duration of intubation and length of stay, without significant side effects, routine supplementation should

Table 2. Literature Review Search Strategy.

Criteria	Search Strategy
Date	March 2016
Inclusion criteria	Subjects: Human, in vivo
	Age: Infants
	Setting: Hospitalized
	Health status: Preterm
	Study design preference: randomized controlled trial, clinical controlled studies, retrospective cohort studies
	Sample size: Any
	Study dropout rate: <20%
	Year range: 2006–2016
	Authorship: If an author is included on >1 review article or primary research article that is similar in content, the most recent review or article will be accepted, and earlier versions will be rejected. If an author is included on >1 review or primary research article and the outcome is different, then both articles may be accepted.
	Language: English
Exclusion criteria	Study dropout rate: >20%
	Year range: Prior to 2006
	Authorship: Studies by same author similar in content
	Language: Non-English
Search terms	"preterm infants," "vitamin A," "bronchopulmonary dysplasia"
Intervention	Vitamin A supplementation
Hits	PubMed: 26
	CINAHL: 4
	Web of Science: 85
Articles to review	PubMed: 3
	CINAHL: 2 (0 excluding duplicates)
	Web of Science: 3 (1 excluding duplicates)
	Total: 4

CINAHL, Cumulative Index to Nursing and Allied Health Literature.

be provided to preterm infants requiring respiratory support or oxygen therapy.[33]

A retrospective cohort study published in 2014 by Gadhia et al looked at the combination therapy of early inhaled nitric oxide (iNO) with vitamin A supplementation for reducing BPD risk.[34] This study utilized data from an earlier multicenter randomized controlled trial (n = 793) investigating the safety and efficacy of iNO in preterm infants.[35] Gadhia et al compared the incidence of BPD among preterm infants receiving iNO alone, iNO with vitamin A, placebo gas alone, and placebo gas with vitamin A. Vitamin A supplementation was provided per each facility's protocol, and infants were stratified according to birth weight category (500–749 g, 750–999 g, and 1000–1250 g).[34] Results reflected a significant reduction in BPD risk (and BPD + mortality risk) among infants with a birth weight of 750–999 g ($P = .01$), as well as significant improvements in developmental scores at 1 year of age among those with birth weights of 500–749 g ($P = .01$). The authors acknowledge that their sample size for those infants with birth weights >1000 g was small and likely underpowered for obtaining significant results; in many facilities, vitamin A supplementation is not routinely given to infants with birth weights >1000 g.[34] The authors concluded that the combination therapy of vitamin A supplementation with early iNO may reduce BPD risk among preterm infants, though prospective studies examining these effects in infants with birth weights <500 g and >1000 g would be beneficial.[34]

Another retrospective cohort study, this one by Uberos et al, examined the effect of IM vitamin A on various complications of prematurity, including BPD, sepsis, retinopathy, and intraventricular hemorrhage.[36] In this study, 154 preterm infants were included for analysis; 60 received supplemental vitamin A. According to the regimen proposed by Kennedy et al, 5000 IU of IM vitamin A was provided 3 times weekly for the first 28 days of life.[37] No statistically significant difference was seen between groups for days on parenteral nutrition or time to achieve full enteral nutrition. Results of this study found no significant difference in BPD risk between those infants who received supplemental vitamin A and those who did not. Of concern, authors did note a trend toward increasing sepsis risk among those receiving supplemental vitamin A. When stratified by weight category, infants with birth weights >1000 g who received IM vitamin A had a significantly higher prevalence of sepsis. On the basis of (1) historical data demonstrating clearer benefits among ELBW infants and those with evidence of vitamin A deficiency, as well as (2) this study's evidence of increased sepsis rates associated with IM vitamin A use among infants >1000 g, the authors concluded that vitamin A supplementation should not be routinely provided to all preterm infants and should be

Table 3. Studies Investigating Vitamin A Supplementation for Bronchopulmonary Dysplasia (BPD) Prevention in Preterm Infants From 2006–2016.[33,34,36,38]

Study[a]					
Purpose	Population	Intervention	Outcomes	Conclusions	Limitations
Kiatchoosakun (2014),[33] randomized controlled trial, class A, rating: + (positive)					
To determine whether vitamin A supplementation prevents BPD in VLBW preterm infants.	Preterm infants (n = 80) weighing <1500 g at birth and who received ventilation or supplemental oxygen at 24 h of age; randomized to 2 groups (n = 40 per group). Mean BW, GA, sex, corticosteroid use, Apgar scores at 1 and 5 min, and respiratory status at 24 h similar between groups.	IM vitamin A, 5000 IU, 3 times weekly × 4 wk vs sham injections (blinded).	Vitamin A supplementation associated with (1) nonsignificant reduction in BPD incidence (P = .21); (2) significant reductions in duration of intubation (P = .03) and LOS (P = .002); (3) nonsignificant reductions in ROP (P = .07), nosocomial sepsis (P = .43), PDA (P = .37), NEC (P = .57).	Vitamin A supplementation significantly reduced duration of intubation and hospital LOS and should be administered routinely to preterm infants requiring respiratory support or oxygen therapy.	Small sample size.
Gadhia (2014),[34] retrospective cohort study, class B, rating: ∅ (neutral)					
To determine whether early iNO with vitamin A supplementation reduces the incidence of BPD in preterm infants.	Preterm infants (n = 793) born 500–1250 g and <34-wk gestational age, with VDRF.	iNO at 5 ppm vs placebo gas in addition to IM vitamin A supplementation per facility protocol: iNO alone (n = 280), iNO + vitamin A (n = 118), placebo gas alone (n = 284), placebo gas + vitamin A (n = 111).	iNO + vitamin A decreased the incidence of BPD and BPD + mortality for infants with BW of 750–999 g (P = .01). iNO + vitamin A improved developmental scores at 1 y for infants with BW of 500–749 g (P = .01).	Combination therapy of iNO with vitamin A supplementation may reduce the risk of BPD for premature infants, compared with iNO therapy alone.	Specifics on vitamin A dose or administration not controlled/ tracked. Small sample size for infants with BW of 500–750 g and >1000 g. Limited information on nutrition support.
Uberos (2014),[36] retrospective cohort study, class B, rating: + (positive)					
To evaluate the effectiveness of vitamin A supplementation for the prevention of prematurity-related complications in VLBW infants.	Preterm infants (n = 154) born <1500 g or <32 wk gestational age.	IM vitamin A, 5000 IU, 3 times weekly during the first 28 d of life (n = 60), vs no supplementation (n = 94).	No significant difference in BPD incidence, mechanical ventilation, days of CPAP, or mortality between groups. Risk of sepsis was up to 3 times higher among the vitamin A group (OR: 3.8, 95% CI: 1.6–8.7).	Universal administration of vitamin A to preterm infants is not justified (due to potential for sepsis risk with no benefit seen in this study), and supplementation should be reserved for ELBW infants with low serum vitamin A levels (<20 μg/dL).	Small sample size.
Moreira (2012),[38] retrospective cohort study, class B, rating: ∅ (neutral)					
To determine if the continued use of vitamin A supplementation in a NICU is warranted, based on effects of supplementation on BPD incidence.	Preterm infants (n = 178) born <1000 g.	Infants born between July 2004 and December 2005 (n = 76) did not receive vitamin A supplementation. Infants born between January 2006 and June 2008 (n = 102) received 3 weekly IM vitamin A doses for the first 28 d of life.	Nonsignificant 11% reduction in BPD incidence with vitamin A supplementation (P = .2).	Vitamin A supplementation resulted in a nonsignificant trend toward reduced BPD incidence in preterm infants, warranting continued use and further trials with larger sample sizes to confirm statistical significance.	Small sample size. Dose not indicated.

BW, birth weight; CPAP, continuous positive airway pressure; ELBW, extremely low birth weight; GA, gestational age; IM, intramuscular; iNO, inhaled nitric oxide; LOS, length of stay; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OR, odds ratio; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; VDRF, ventilator dependent respiratory failure; VLBW, very low birth weight.

[a]Based on the Academy of Nutrition and Dietetics' Evidence Analysis rating system.

reserved only for those infants with ELBWs and evidence of deficiency.[36]

Moreira et al also utilized a retrospective cohort design to determine whether continued use of vitamin A supplementation in a facility was warranted, based on the effect of vitamin A supplementation on BPD risk.[38] The authors hypothesized that the major improvements seen in their NICU (including a reduction in BPD incidence) could be attributed to the introduction of nasal continuous positive airway pressure, reduced oxygen exposure, and improvements in nutrition delivery, rather than vitamin A supplementation. Infant cases (n = 178) were retrospectively analyzed, and those born between July 2004 and December 2005 (n = 76; ie, before the introduction of vitamin A supplementation) were compared with those born between January 2006 and June 2008 (n = 102; ie, after the introduction of vitamin A supplementation). The only difference in treatment between the 2 groups was the use of IM vitamin A, 3 times weekly for the first 28 days of life. Infants receiving IM vitamin A supplementation experienced an 11% reduction in BPD incidence ($P = .2$). Although these results were not statistically significant, the authors concluded that the use of vitamin A within their facility is still beneficial, and larger trials may show more statistically significant results.[38]

Discussion

In this review, only 1 of 4 studies showed a significant reduction in BPD incidence associated with vitamin A supplementation (in conjunction with iNO).[34] Two of 4 studies showed a nonsignificant reduction in BPD incidence but indicated that sample size may have limited statistical significance.[33,38] Only 1 study (Uberos et al) found any adverse side effects of vitamin A supplementation, with a 3-fold higher risk of sepsis seen in infants (weighing >1000 g at birth) receiving vitamin A.[36] Despite the fact that only 1 study found statistically significant improvements, the authors of 3 of the 4 studies concluded that continued administration of vitamin A supplementation to preterm infants is warranted.[33,34,38]

Although adverse side effects of vitamin A supplementation appeared to be minimal in this analysis (with the exception of 1 study), the risk of toxicity must be considered when determining optimal dosing. High vitamin A supplementation has been associated with bulging fontanelles in some infants (a potential sign of intracranial hypertension), but this effect appears to be transient and without long-term consequences. Increased circulating vitamin A levels are thought to cause a modest and temporary increase in cerebrospinal fluid volume, which may result in fullness of the fontanelles.[39-43] Other potential signs and symptoms of vitamin A toxicity (in pediatric and/or adult populations) include nausea, vomiting, weight loss, fatigue, irritability, cephalgia, diplopia, ostealgia, alopecia, skin lesions, and cheilosis.[44] However, as much as a single 50,000-IU dose of oral vitamin A has been provided to term infants without adverse effects.[45,46] Likewise, parenteral vitamin A in doses up to 8500 IU/kg/d has not been associated with negative outcomes.[28,47] For IM vitamin A supplementation, 5000 IU 3 times weekly for 4 weeks (for a total of 12 doses) is currently the most commonly used regimen. A study by Ambalavanan et al compared 3 dosing regimens (5000 IU 3 times weekly for 4 weeks, 10,000 IU 3 times weekly for 4 weeks, and 15,000 IU once per week for 4 weeks) for their effects on vitamin A status and clinical outcomes in ELBW infants.[48] As compared with the standard regimen, the higher dose (10,000 IU) did not affect vitamin A status or clinical outcomes, and the once-weekly dosing worsened vitamin A deficiency. Thus, the authors concluded that the standard regimen of 5000 IU 3 times weekly for 4 weeks is still the best option for preterm infants.[48] Weight-based dosing may not be appropriate for this population, as smaller babies typically have more significant deficiency and a higher risk of lung disease.[28,48]

Table 4. Infant Birth Weight Classifications.[49]

Classification	Weight, g
Low birth weight	<2500
Very low birth weight	<1500
Extremely low birth weight	<1000

The results of this analysis suggest that the effect of vitamin A supplementation on BPD risk may be more pronounced in infants with lower birth weights. Weight categorization is reviewed in Table 4.[49] Ambalavanan et al indicate that this enhanced effect may be seen in preterm infants with lower birth weights due to a higher incidence of vitamin A deficiency or a higher risk of BPD in this population.[48] Within this review, Gadhia et al found a smaller impact of vitamin A supplementation on infants weighing >1000 g at birth; however, the authors indicated that the number of subjects within this classification was likely underpowered (as vitamin A supplementation was based on each facility's protocol, and many facilities do not routinely supplement vitamin A for those infants with birth weights >1000 g).[34] Uberos et al actually found negative effects (an increased sepsis risk) with vitamin A supplementation in infants weighing >1000 g at birth.[36]

In a subgroup analysis from the original NICHD trial,[28] Londhe et al sought to determine whether preterm infants who were small for gestational age (SGA) experienced a greater reduction in BPD risk than ELBW preterm infants who were appropriate for gestational age.[50] Results from this analysis indicated a trend toward an increased risk for BPD and mortality in the SGA group, though any difference in the effect of vitamin A supplementation did not reach statistical significance. The authors concluded that although their analysis did not yield statistically significant results, this population may be more vulnerable to BPD risk, and larger studies investigating optimal vitamin A supplementation for SGA preterm infants are needed.[50]

Due to a number of confounding factors, it can be challenging to determine the effect of vitamin A supplementation on BPD incidence when reviewing historical data. A national shortage of vitamin A dramatically reduced usage between 2010 and 2014 in the United States.[51] A multicenter retrospective cohort study of infants with birth weights between 401–1000 g (n = 7925) who were discharged from the NICU between January 1, 2010, and June 30, 2012 was completed to determine the impact of the vitamin A shortage on clinical outcomes.[51] Results indicated no significant change in BPD rates ($P = .40$) despite a major reduction in vitamin A use (27.2% to 2.1%) during the study period. However, when results were stratified according to study facility, significant variability was seen among centers (with birth in low- and medium-use centers associated with reduced mortality and BPD risk). The authors concluded that the vitamin A shortage did not appear to affect BPD risk among preterm neonates, although there was some variance in outcomes seen among study centers.[51] No other data examining the effect of the shortage of vitamin A on BPD incidence in preterm infants are currently available.

Another major confounding factor that may have affected BPD incidence in recent years is oxygen therapy. A 2010 study published in the *New England Journal of Medicine* found that higher oxygen saturation targets (91%–95%) were associated with reduced mortality among preterm infants, as compared with lower targets (85%–89%).[52] However, higher early oxygen exposure may also predispose preterm infants to BPD.[53] It is unclear whether the findings supporting higher oxygen saturation targets have resulted in a widespread change in respiratory therapy for preterm infants and whether this may have affected BPD rates. However, as multiple factors have potentially caused recent changes in clinical practice and may have affected BPD rates, a large multicenter randomized clinical trial is warranted to clearly determine the effect of vitamin A supplementation on BPD risk.

Conclusion

In conclusion, the results of this review suggest that IM vitamin A may have a modest benefit in reducing BPD risk among preterm infants. Significant BPD risk reduction was seen in only 1 study reviewed; however, small sample sizes may not have been adequately powered to reflect significant improvements in the others. Because some benefit has been seen with the use of IM vitamin A and given that the risk appears to be minimal, continued supplementation for preterm infants is still warranted. However, because 1 study found an increased sepsis risk associated with vitamin A supplementation in infants weighing >1000 g, preference should be given to those infants weighing <1000 g and/or with evidence of deficiency. Larger trials with a greater focus on stratifying results by birth weight, as well as determining optimal dosing and minimizing the number of doses as feasible, are needed for more definitive recommendations to be made. A meta-analysis was outside the scope of this article; however, in addition to larger trials, a meta-analysis on this topic would be beneficial to better illustrate the statistical significance of the available data.

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Statement of Authorship

All authors contributed to the conception/design of the research; and E. Schwartz contributed to the acquisition, analysis, and interpretation of the data and drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Systematic Review of the Human Milk Microbiota

John L. Fitzstevens[1]; Kelsey C. Smith, MA[2,3]; James I. Hagadorn, MD[2,3,4]; Melissa J. Caimano, PhD[5,6]; Adam P. Matson, MD[3,4,7]; and Elizabeth A. Brownell, PhD[2,3,4]

Abstract

Human milk–associated microbes are among the first to colonize the infant gut and may help to shape both short- and long-term infant health outcomes. We performed a systematic review to characterize the microbiota of human milk. Relevant primary studies were identified through a comprehensive search of PubMed (January 1, 1964, to June 31, 2015). Included studies were conducted among healthy mothers, were written in English, identified bacteria in human milk, used culture-independent methods, and reported primary results at the genus level. Twelve studies satisfied inclusion criteria. All varied in geographic location and human milk collection/storage/analytic methods. *Streptococcus* was identified in human milk samples in 11 studies (91.6%) and *Staphylococcus* in 10 (83.3%); both were predominant genera in 6 (50%). Eight of the 12 studies used conventional ribosomal RNA (rRNA) polymerase chain reaction (PCR), of which 7 (87.5%) identified *Streptococcus* and 6 (80%) identified *Staphylococcus* as present. Of these 8 studies, 2 (25%) identified *Streptococcus* and *Staphylococcus* as predominant genera. Four of the 12 studies used next-generation sequencing (NGS), all of which identified *Streptococcus* and *Staphylococcus* as present and predominant genera. Relative to conventional rRNA PCR, NGS is a more sensitive method to identify/quantify bacterial genera in human milk, suggesting the predominance of *Streptococcus* and *Staphylococcus* may be underestimated in studies using older methods. These genera, *Streptococcus* and *Staphylococcus*, may be universally predominant in human milk, regardless of differences in geographic location or analytic methods. Primary studies designed to evaluate the effect of these 2 genera on short- and long-term infant outcomes are warranted. (*Nutr Clin Pract*.2017;32:354-364)

Keywords

breast milk; human milk; microbiota; microbiome; human microbiome; metagenome

Breastfed infants have a decreased risk of developing respiratory tract infections, atopic dermatitis, asthma, obesity, type 1 and 2 diabetes, necrotizing enterocolitis, gastroenteritis, and sudden infant death syndrome.[1,2] Human milk is nutrient rich,[1] and bacterial communities have been identified in human milk by both culture-dependent and culture-independent analyses.[3,4] Human milk has the potential to modulate colonization and development of the immature newborn gut[5] through the transmission of milk-based bacteria.[6,7] As a result, the bacterial content of human milk may directly affect short- and long-term infant health outcomes.[8]

The mission of the Human Microbiome Project is to characterize the human microbiome from multiple body sites, but the investigators did not include human milk as one of the 18 anatomical regions or body sites of interest.[9] Nonetheless, independent studies have analyzed the human milk microbiota.[3,6,7,10–26] Early studies using cultured breast milk isolated only a limited number of genera.[6] Subsequent development of culture-independent methods has allowed for a more complete understanding of the composition and diversity of microbiota present in human milk.* Using ribosomal RNA (rRNA) polymerase chain reaction (PCR), Hunt et al[13] identified a "core" milk microbiota consisting of 9 bacterial genera in milk collected from 16 mothers, while Jiménez et al[24] identified an alternate core microbiota consisting of 7 genera in samples collected from 10 mothers. Only *Staphylococcus*, *Streptococcus*, and *Propionibacterium* were similarly reported in both studies as predominant genera in maternal milk.[13,24] This may be the result of dietary, genetic, or environmental differences affecting the human milk microbiota.[3,13]

This systematic review sought to characterize the diversity and commonalities of the human milk microbiota by

*References 6, 7, 10, 13–15, 17, 20, 24, 26,27.

From the [1]Department of Biology, Swarthmore College, Swarthmore, Pennsylvania, USA; [2]Connecticut Human Milk Research Center, Connecticut Children's Medical Center, Hartford, Connecticut, USA; [3]Division of Neonatology, Connecticut Children's Medical Center, Hartford, Connecticut, USA; [4]Department of Pediatrics, University of Connecticut School of Medicine, Farmington, Connecticut, USA; [5]Department of Molecular Biology and Biophysics, University of Connecticut Health Center, Farmington, Connecticut, USA; [6]Department of Medicine, University of Connecticut Health Center, Farmington, Connecticut, USA; and [7]Department of Immunology, University of Connecticut School of Medicine, Farmington, Connecticut, USA.

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Corresponding Author:
Elizabeth A. Brownell, PhD, Connecticut Human Milk Research Center
Division of Neonatology, Connecticut Children's Medical Center, 282 Washington St, Hartford CT 06106, USA.
Email: ebrownell@connecticutchildrens.org

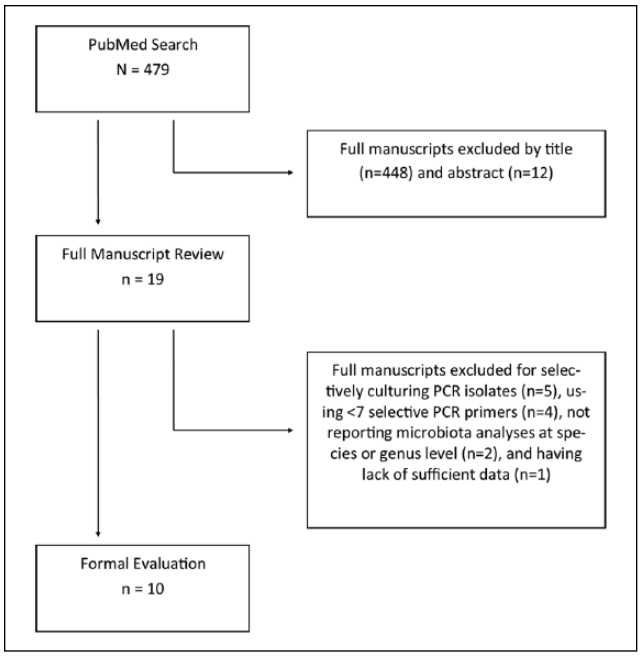

Figure 1. Literature search flow diagram. PCR, polymerase chain reaction.

synthesizing data derived from culture-independent methods using samples obtained from various geographic locations.

Methods

We identified all primary studies indexed in PubMed from January 1, 1964, through June 30, 2015, that described the diversity of healthy mothers' milk microbiota. Search terms included the following: microbiome OR microbiota OR anaerobic OR anaerobe OR metagenome AND (human milk OR breast milk).

We identified eligible studies for this systematic review using the following inclusion criteria: (1) primary study, (2) written in English, (3) exclusive use of human subjects, (4) investigated bacterial diversity and composition of human milk, (5) used culture-independent methods, and (6) reporting primary results at the genus level. The following exclusion criteria eliminated studies from the review: (1) exclusive assessment of the microbiota of colostrum and (2) incomplete/insufficient data set reported.

Two authors independently reviewed PubMed search results. Reviewers assessed each title, evaluated abstracts as necessary, and considered the study for full review. Any disagreements in either the title/abstract or the full manuscript review phases were resolved by consensus. All eligible studies were formally evaluated and included in this systematic review.

Results

The PubMed search yielded 479 articles (Figure 1). We excluded 448 articles by title and 12 by abstract review; 19 articles qualified for full manuscript review. Of those 19, we excluded 5 that did not evaluate the bacterial diversity of human milk, 1 for nonindependent evaluation of the human milk microbiota, and 1 for having an incomplete data set; 12 articles qualified for formal evaluation.

Characteristics of formally evaluated studies are presented in Table 1. Studies were conducted in Spain, Finland, Turkey, Canada, Switzerland, and the United States. Six studies evaluated healthy mothers exclusively, while the remaining 6 compared healthy mothers with mothers who were overweight, were undergoing chemotherapy, and had celiac disease, mastitis, or breast milk jaundice. The definition of maternal health status varied among studies; 6 studies cited the absence of medical conditions,[10,12,21,22,24,26] 1 used maternal self-report,[13] and 5 did not specify how maternal health was defined.[4,6,17,19,20] Aseptic milk collection techniques differed with respect to use of chlorhexidine[21]; a combination of soap, sterile water, and chlorhexidine[6,12,24]; iodine[13,22,26]; aseptic soap[28]; sterile swabs[17]; sterile gloves[19]; sterile collection bag[20]; or undefined.[16] In addition, studies varied with respect to microbial detection methods. Eight studies[6,12,16,17,19,21,22,26] (67%) used conventional rRNA PCR, whereas 4 studies[10,13,20,24] (33%) used next-generation sequencing (NGS), which included 454-pyrosequencing using an Illumina (Illumina Inc, San Diego, CA) platform. As well, the collection timeframe of the included milk samples varied from 4 days postpartum to 6 months postpartum,[4,12,19–22,26] while 5 studies did not identify the postpartum day milk samples were collected.[6,13,17,24,28]

Microbial Presence

Microbial presence was defined by included studies as the genera or species identified in the human milk samples. The genera *Streptococcus* and *Lactobacillus* were identified in 11 studies (91.6%), *Staphylococcus* in 10 studies (83.3%), *Bifidobacterium* in 9 studies (75%), *Enterococcus* in 8 studies (66.7%), and *Propionibacterium* in 6 studies (50%) (Table 2). Differences in methodology resulted in inconsistent detection of bacterial diversity of human milk. Using conventional rRNA PCR, *Lactobacillus* was identified in all 8 studies (100%), *Bifidobacterium* and *Streptococcus* in 7 studies (87.5%), *Staphylococcus* in 6 studies (75%), and *Enterococcus* in 4 studies (50%). NGS methods yielded detection of *Streptococcus*, *Staphylococcus*, *Enterococcus*, and *Propionibacterium* in all 4 studies (100%), *Lactobacillus* in 3 studies (75%), and *Bifidobacterium* in 2 studies (50%). Deeper level sequencing, investigated at the species level, found no microbial patterns across all included studies.

Microbial Predominance

Included studies defined microbial predominance as the most abundant genera or species populating the human milk microbiota. The genera *Streptococcus* and *Staphylococcus* were

Table 1. Microbiota of Human Milk: Characteristics of Qualifying Studies.

Reference, Location	Research Question	Sample Size	Study Population	Collection and Storage	Analysis	Results: Observed Biodiversity Among Healthy Mothers	Conclusion
Pre-Next-Generation Sequencing							
Martín et al,[16] 2007, Spain	Evaluate the dominant bacteria in HM of mothers with vaginal and cesarean births	n = 4	Healthy mothers	Aseptically collected 7 days postpartum; icebox and then –80°C storage	PCR with DGGE[a]	Predominant: *Streptococcus* and *Staphylococcus; Pseudomonas* in vaginal deliveries	HM is a source of commensal bacteria for the infant gut.
Collado et al,[6] 2009, Spain	Characterize the HM microbiota	n = 50	Healthy mothers	HE and aseptically collected; –4°C and then –80°C storage	qRTi-PCR[b]	Predominant: *Bifidobacterium*, *Lactobacillus*, *Staphylococcus*, and *Streptococcus*	HM contains an abundance of bacterial DNA.
Cabrera-Rubio et al,[26] 2012, Finland	Identify factors influencing HM bacteria and compare bacteria of different body sites	n = 18	8 healthy and 10 overweight mothers	Aseptically collected within 2 days and at 1 and 6 months postpartum; –20°C storage	qPCR, 3 secondary PCRs/sample[c]	Predominant: *Weiselle* and *Leuconostoc;* increase in abundance of *Veillonella*, *Leptotrichia*, and *Prevotella* in 1- and 6-month milk samples	The HM microbiome changes over lactation stages and differs by maternal weight and delivery mode.
Collado et al,[22] 2012, Finland	Analyze maternal influences—namely, weight—on HM microbiota and cytokines	n = 56	34 normal-weight and 22 overweight mothers	HE aseptically collected at 24–48 hours, 1 and 6 months postpartum; –20°C storage	DNA extraction and qRTi-PCR[b]	No predominant genera observed; present: *Bifidobacterium* and *Streptococcus* were observed in 100% of 1- and 6-month milk samples[d]	HM is the single most important postpartum element in metabolic and immunological programming of the infant's health.
Tuzun et al,[12] 2013, Turkey	Evaluate the effect of breast milk jaundice development on HM and infant feces' microbiota	n = 60	30 healthy and 30 mothers with breast milk jaundice	HE and aseptically bilaterally collected between 1 and 28 days postpartum; first ice and then –70°C storage[e]	Real-time PCR[b]	Predominant: *Bifidobacterium*[e]	HM microbial content may play a role in breast milk jaundice.
Urbaniak et al,[17] 2014, Canada	Investigate chemotherapy's effects on HM's microbiota and metabolome (case study)	n = 9	8 healthy mothers and 1 undergoing chemotherapy	Aseptically collected over 4 months; initial ice and then –20°C storage	PCR and gas chromatography/ mass spectrometry[f]	No predominant genera observed; identified a wide microbial diversity in healthy mom's milk[e]	A wide microbial diversity was identified in healthy mothers' milk.
Khodayar-Parto et al,[21] 2014, Spain	Examine the effects of lactation stage, gestational age, and delivery mode on HM microbiota	n = 32	Healthy mothers, 13 with term and 19 with preterm deliveries	Mothers EE and collected HM; 3 samples taken at days 1–5, 6–15, and 17; –20°C storage	DNA extraction and qPCR[b]	*Bifidobacterium*, *Lactobacillus*, *Staphylococcus*, and *Enterococcus* identified in all mature milk samples from mothers with term and preterm deliveries	Lactation stage, degree of prematurity, gestational age, and delivery mode influence HM microbiota.
Olivares et al,[19] 2015, Spain	Describe how celiac disease alters HM composition and microbiota	n = 24	12 healthy mothers and 12 with celiac disease	Mothers HE and aseptically collected milk at early feed; –20°C storage	Conventional, qRTi-PCR CE-LIF[b]	Predominant: *Bifidobacterium*[d]	Mothers with celiac disease have a decreased abundance of immunoprotective compounds and certain bacteria than healthy mothers.

(continued)

Table 1. (continued)

Reference, Location	Research Question	Sample Size	Study Population	Collection and Storage	Analysis	Results: Observed Biodiversity Among Healthy Mothers	Conclusion
				Next-Generation Sequencing			
Hunt et al,[13] 2011, United States	Evaluate stability and diversity of HM bacteria over time	n = 16	Healthy mothers	Mother EE, aseptically collected 3 times over 4 weeks; –20°C storage	Pyrosequencing[c]	9 core genera OTUs present in all samples: *Staphylococcus*, *Streptococcus*, *Serratia*, *Pseudomonas*, *Corynebacterium*, *Ralstonia*, *Propionibacterium*, *Sphingomonas*, *Bradyrhizobium*	HM contains a diverse and complex bacterial community.
Jost et al,[10] 2013, Switzerland	Investigate bacterial diversity of HM of mothers who gave vaginal birth	n = 7	Healthy mothers	Aseptically collected at 3 time points; –80°C storage	Cultures, Sanger sequencing, 454-pyrosequencing, 16S ribosomal RNA gene sequencing[g]	Predominant: *Staphylococcus*, *Streptococcus*, and *Propionibacterium*	HM may significantly influence infant gut colonization and immune system.
Ward et al,[20] 2013, Canada	Examine the HM metagenome	n = 10	Healthy mothers	Aseptically collected unsterilized breast milk 9–30 days postpartum; pooled samples; –70°C storage	Illumina sequencing[b]	Predominant: *Pseudomonas*, *Staphylococcus*, and *Streptococcus*	Diversity of bacterial may be beneficial; benefits are not associated with particular genera or species.
Jiménez et al,[24] 2015, Spain	Investigate the effects of mastitis on HM's metagenome	n = 20	10 healthy mothers and 10 with mastitis	HE and aseptically collected	Cultures, shotgun libraries from 454-pyrosequenced DNA[b]	Predominant: *Bacteroides*, *Bifidobacterium*, *Burkholderia*, *Faecalibacterium*, *Lactobacillus*, *Novosphingobium*, *Propionibacterium*, *Pseudomonas*, *Ruminococcus*, *Sphingomonas*, *Sphingobium*, *Sphingopyxis*, *Staphylococcus*, and *Streptococcus*	Relative to healthy mothers, women with mastitis have different HM metagenomes.

CE-LIF, electrophoresis-laser-induced fluorescence; DGGE, denaturing gradient gel electrophoresis; EE, electric expression; HE, hand expression; HM, human milk; OTU, operational taxonomic unit; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; qRTi, quantitative real time.
[a]PCR amplification of the V6–V8 regions of 16S ribosomal RNA.
[b]Authors did not specify which hypervariable region was amplified.
[c]Targeted amplification of the V1 and V2 regions of 16S ribosomal RNA.
[d]Authors reported data on additional milk components.
[e]Authors reported additional data on feces components.
[f]Targeted amplification of the V6 region of 16S ribosomal RNA.
[g]Targeted amplification of the V5–V6 regions of 16S ribosomal RNA.

Table 2. Bacterial Diversity of Human Milk From Healthy Mothers Stratified by Sequencing Method.[a]

Genus	Species	Martín et al[16]	Collado et al[6]	Cabrera-Rubio et al[26]	Collado et al[22]	Tuzun et al[12]	Urbaniak et al[17]	Khodayar-Parto et al[21]	Olivares et al[19]	Hunt et al[13]	Jost et al[10]	Ward et al[20]	Jiménez et al[24]
		Pre-Next-Generation Sequencing								Next-Generation Sequencing			
Acinetobacter		y		y			y						
	calcoaceticus	y											
Actinomyces										y			
Akkermansia					y							y	
	muciniphila				y								
Anoxybacillus-Bacillus							y						
Atopobium							y						
Bacillus							y						
Bacteroides[b]			y										y[c]
Bifidobacterium			y[c]	y	y[d]	y[c]	y	y[e]	y[c]		y		y
	bifidum					y			y				
	breve								y		y		y
	fragilis								y				
	longum					y							y
Bradyrhizobium[f]										y[c]			
Brevundimonas-Caulobacter							y						
	diminuta						y						
Burkholderia[b]													y[c]
Campylobacter												y	
Candidatus												y	
Candidatus Phytoplasma													y
Carnobacterium				y									
Citrobacter				y									
Cloacibacterium							y						
Clostridium				y	y				y				
	coccoides			y	y				y				
	IV		y										
	XIVa		y										
	XIVb		y										
Corynebacterium[f]				y			y			y[c]		y	y
Edwardsiella												y	
Enterococcus		y	y	y	y			y[g]	y		y		y
	faecalis	y									y		

(continued)

Table 2. (continued)

Genus	Species	Martín et al[16]	Collado et al[6]	Cabrera-Rubio et al[26]	Collado et al[22]	Tuzun et al[12]	Urbaniak et al[17]	Khodayar-Parto et al[21]	Olivares et al[19]	Hunt et al[13]	Jost et al[10]	Ward et al[20]	Jiménez et al[24]
		Pre-Next-Generation Sequencing								Next-Generation Sequencing			
	faecium	y											
	gallinarum										y		
Escherichia		y									y		
	coli	y											
Eubacterium							y						
Faecalibacterium[b]							y						y[c]
	prausnitzii						y						
Finegoldia							y					y	
Flavobacterium-Cytophaga							y						
Gardnerella							y						
Gemella		y					y			y			
	haemolysans	y											
Granulicatella										y			
Klebsiella											y		
	pneumoniae										y		
Lactobacillus[b]		y	y[c]	y	y	y	y	y[g]	y		y	y	y[c]
	brevis										y		
	delbrueckii						y						
	fermentum					y							
	gasseri					y					y		
	plantarum	y				y							
	rhamnosus					y							
Lactococcus		y		y									
	lactis	y											
Leptotrichia				y									
Leuconostoc		y		y[c]									
	citreum	y											
Lysinibacillus				y									
Methylophilus							y						
Mycoplasma												y	
Neisseria													y
Novosphingobium													y
Pantoea												y	
Parabacteroides													y
Peredibacter							y						

(continued)

Table 2. (continued)

Genus	Species	Martín et al[16]	Collado et al[6]	Cabrera-Rubio et al[26]	Collado et al[22]	Tuzun et al[12]	Urbaniak et al[17]	Khodayar-Parto et al[21]	Olivares et al[19]	Hunt et al[13]	Jost et al[10]	Ward et al[20]	Jiménez et al[24]
		Pre-Next-Generation Sequencing								Next-Generation Sequencing			
Petrobacter							y						
Porphyrobacter							y						
Porphyromonas							y						
	synxantha	y											
Prevotella				y			y			y			
Propionibacterium[b,f]		y					y			y[c]	y[c]	y	y[c]
	acnes	y									y		
	granulosum										y		
Pseudomonas[f]		y[h]					y			y[c]		y[c]	y
Ralstonia[f]										y[c]			
Rhizobium-Agrobacterium							y						
Rothia							y			y	y		
	mucilaginosa										y		
Roseburia													y
Ruminococcus[b]							y						y[c]
	gnavus						y						
Schlegelella							y						
Serratia[f]		y								y[c]			
	proteamaculans	y											
Shigella											y		
Sphingobacterium							y						
Sphingomonas[f] *Sphingobium*							y			y[c]			y
Sphingopyxis													y
Staphylococcus[b,f]		y[c]	y[c]	y	y		y	y[e]		y[c]	y[c]	y[c]	y[c]
	aureus			y	y						y		
	epidermidis	y									y		
	haemolyticus										y		
	hominis	y									y		
	lugdunensis										y		
	pasteuri										y		
	salivarius	y											
	warneri										y		
Stenotrophomonas				y									
Streptococcus[b,f]		y[c]	y[c]	y	y[d]		y	y	y	y[c]	y[c]	y[c]	y[c]
	atypical-dispar-parvula										y		

(continued)

Table 2. (continued)

Genus	Species	Martín et al[16]	Collado et al[6]	Cabrera-Rubio et al[26]	Collado et al[22]	Tuzun et al[12]	Urbaniak et al[17]	Khodayar-Parto et al[21]	Olivares et al[19]	Hunt et al[13]	Jost et al[10]	Ward et al[20]	Jiménez et al[24]
		Pre-Next-Generation Sequencing								Next-Generation Sequencing			
	mitis	y									y		
	parasanguinis	y											
	pneumoniae	y											
	salivarius	y									y		
	thermophilus						y				y		
	vestibularis										y		
Thermus							y						
Veillonella		y		y							y		
Weissella		y		y[c]									
	cibaria	y											
	confusa	y											

[a]Genera are listed in alphabetical order; species are listed in alphabetical order by genus. y, genera or species identified as present.
[b]Core 7.[24]
[c]Genera or species identified as a predominant.
[d]Authors did not denote prevalent genera, but these genera were identified in 100% human milk samples measured at 1-month and 6-month milk samples among normal-weight mothers.
[e]Identified in 100% of samples of both term and preterm mature milk.
[f]Core 9. Hunt et al[13] misreported the family Bradyrhizobiaceae as a part of the core 9 genera, instead of the genus *Bradyrhizobium*, which we have classified as "core 9" above.
[g]Identified in 100% of samples from transitional and mature milk in both preterm and term.
[h]Identified as present in cesarean section birth but predominant in vaginal births.

predominant in 6 of the 12 formally evaluated studies (50%) (Table 2). *Bifidobacterium* was defined as predominant in 3 studies (25%), *Propionibacterium* in 3 studies (25%), *Lactobacillus* in 2 studies (17%), and *Enterococcus* in 0 studies (0%). Again, differences in methodological approaches were observed. Using a conventional PCR-based approach, *Streptococcus* and *Staphylococcus* were predominant in 2 studies (25%), *Bifidobacterium* in 3 studies (38%), *Propionibacterium* in 0 studies (0%), *Lactobacillus* in 1 study (13%), and *Enterococcus* in 0 studies (0%). Using NGS, *Streptococcus* and *Staphylococcus* were predominant in all 4 studies (100%), *Bifidobacterium* in 0 studies (0%), *Propionibacterium* in 3 studies (75%), *Lactobacillus* in 1 study (25%), and *Enterococcus* in 0 studies (0%). Deeper level sequencing, investigated at the species level, found no predominant species-specific microbial patterns.

Discussion

Studies included in this systematic review varied with respect to geographic location and methods of milk collection, storage, and analysis. *Streptococcus* and *Staphylococcus* were the predominant genera in 6 of the 12 studies (50%) and in all 4 (100%) of those using NGS methods. These 2 genera, *Streptococcus* and *Staphylococcus*, appear to be widely predominant in human milk without regard to differences in geographic location or analytic methods.

Our findings identified only 2 consistently predominant genera that contradict existing research reporting a "core 9" and "core 7" human milk microbiota.[13,24] Jiménez et al[24] and Hunt et al[13] identified two diverse core human milk microbiomes. Using shotgun amplification, Jiménez et al identified a healthy core human milk microbiome that included the genera *Staphylococcus*, *Streptococcus*, *Bacteroides*, *Faecalibacterium*, *Ruminococcus*, *Lactobacillus*, and *Propionibacterium*. At the species level, there was a high degree of interindividual variability observed among healthy women. Using NGS, Hunt et al identified a set of 9 operational taxonomic units that were present in all milk samples collected: *Staphylococcus*, *Streptococcus*, *Serratia*, *Pseudomonas*, *Corynebacterium*, *Ralstonia*, *Propionibacterium*, *Sphingomonas*, and *Bradyrhizobiaceae*; bacterial species were not identified.[13] Between these 2 studies, *Staphylococcus*, *Streptococcus*, and *Propionibacterium* were the only genera commonly reported as predominant in both identified core human milk microbiotas. This suggests that additional genera identified as a part of the "core 9" and "core 7" may not be consistently represented as predominant genera in the human milk microbiota. Identification of the "core 9" and "core 7" used culture-independent methods but analyzed mother's milk from different geographic locations with variable milk collection, storage, and analytic methods. Using NGS, Hunt et al amplified the V1–V2 hypervariable region of the 16S rRNA gene. Jiménez and colleagues did not specify which hypervariable region was amplified, but taxonomy was assigned based on shotgun sequencing. Despite the methodological differences in these studies, their mutual identification of *Streptococcus* and *Staphylococcus* as part of the "core" genera is consistent with our findings and suggests that these genera may be widely predominant in human milk.

The ability to detect bacterial diversity in human milk may be dependent on milk collection techniques and analytic methods. By cloning and sequencing DNA, PCR is an effective way to characterize microbial communities.[27] However, recent literature suggests that certain genera are better identified by primers targeting specific 16S variable gene regions.[29,30] Observed between-study differences may be attributable to variations in regional amplification. Relative to conventional rRNA PCR, NGS is a more sensitive and less biased analytic method for identifying and quantifying bacterial genera in human milk.[31] This suggests that the presence/predominance of *Streptococcus* and *Staphylococcus* may be underestimated in studies using conventional methods.

The phylogeny and biological significance of the human milk microbiota have been described in detail elsewhere.[8,28,32,33] The entero-mammary pathway suggests that microbes located in the maternal gut translocate to the mammary glands and, upon milk consumption, colonize the infant gut.[8,28,32,33] The human milk microbiota may be involved in the development of infant innate immunity and serve as a functional link between maternal and infant gut microbiota.[8,33] This relationship is multifactorial and dependent on many potential confounding factors such as delivery mode,[21,34–39] antibiotic use,[15,18] and maternal obesity.[22,26,40] Infants exclusively breastfed have been shown to have a less diverse and rich intestinal microbiota in comparison to infants formula fed.[41,42] This decreased diversity and richness may be attributed to microbes present in human milk and human milk oligosaccharides[41,42] potentially influencing the colonization of the infant gut. The infant gut microbiota has been associated with neurodevelopmental outcomes and may play a role in early brain development.[43] The human milk microbiota contains some of the first microbes to be introduced into the infant gut, thus potentially playing a large role in the colonization of the infant gut and development of the immune system.[26] Interventions designed to modify maternal gut microbiota (eg, diet, nutrition supplements) may affect human milk microbiota and subsequently influence infant gut microbiota and alter infant health outcomes.[33,44,45]

Our study has several strengths worth highlighting. Both reviewers independently conducted a PubMed search and evaluated qualifying manuscripts. This systematic approach, designed to maximize reliable results, ensured precise study identification and data abstraction processes. Our inclusion criteria were broad and not restricted to specific variations of culture-independent methods. This increased the generalizability of our findings, allowing a comparison of studies using both conventional PCR and NGS methods. By design, our study also included only those investigating the bacterial diversity of the human milk microbiota, thus enabling an unbiased synthesis of predominant bacterial diversity.

The observed results are subject to several limitations. First, reviewers were not blinded to the purpose of this study. This may have introduced a nondifferential bias, leading to either overinterpretation or underinterpretation of common present or predominant genera. Second, to maximize the abstracted study characteristics, only studies written in English were included in this systematic review. Third, to ensure all identified studies were peer-reviewed, we did not include published abstracts presented at previous academic meetings. Fourth, given the descriptive nature of our research question, we abstracted and evaluated study results but did not conduct formal evaluations of study design, methodological rigor, or research methods. This descriptive approach was purposeful in design to be more inclusive, thus allowing synthesis of studies that used either conventional PCR or NGS.

Conclusion

In summary, this systematic review of the literature reports that the genera *Streptococcus* and *Staphylococcus* are the predominant genera in the human milk microbiota. We suggest that these 2 genera may be universally predominant in the human milk microbiota, independent of geographic location or milk collection technique and may have been underestimated in previous work using conventional PCR methods. Future research to confirm these findings and to further clarify the effects of human milk microbes on infant short-term and long-term health outcomes should use NGS methods to maximize detectable bacterial diversity.

Statement of Authorship

J. L. Fitzstevens conceived and executed the study, abstracted data, drafted the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. K. C. Smith conceived and executed the study, abstracted data, reviewed and revised the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. J. I. Hagadorn conceived and executed the study, reviewed and revised the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. M. J. Caimano conceived and executed the study, reviewed and revised the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. A. P. Matson conceived and executed the study, reviewed and revised the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. E. A. Brownell conceived and executed the study, supervised the overall study and coordinated the interpretation of results, reviewed and revised the manuscript, approved the final submission, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Review

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Recommending Small, Frequent Meals in the Clinical Care of Adults: A Review of the Evidence and Important Considerations

Hassan S. Dashti, PhD[1]; and Kris M. Mogensen, MS, RD, LDN, CNSC[1]

Abstract

Small, frequent meals (SFMs) are a dietary regimen characterized by multiple small eating episodes throughout the day. Clinical nutrition guidelines recommend SFMs (eg, 6–10 meals) to patients experiencing common symptoms (eg, early satiety) and gastrointestinal-related symptoms. However, whether the provision of SFMs palliatively improves morbidity of nutritionally at-risk individuals has yet to be elucidated. This narrative review summarizes current clinical guidelines recommending SFMs for the management of diseases in adult patients (≥18 years), with supporting experimental and epidemiologic evidence, and it provides suggestions pertaining to this recommendation by drawing on potential considerations from investigations in healthy adults. Limited studies suggest that SFMs may promote higher energy and fluid intakes, reduce gastrointestinal-related symptoms (including vomiting, bloating, and fullness), and prevent postprandial hypotension in patients with primary autonomic failure. Potential health complications related to SFMs include unwarranted weight gain, suboptimal nutrition quality, later meal times, sleep disturbances, limited intermittent fasting, and disordered eating that may exacerbate the underlying disease or related symptoms. Thus, it is prudent for health professionals to supplement SFM recommendations with additional guidance on meal size, frequency, and timing, with a strong emphasis on healthy meal quality. Future research should recognize a standardized definition for SFMs and utilize better methods to obtain reliable data on meal patterns. (*Nutr Clin Pract*. 2017;32:365-377)

Keywords

circadian rhythm; sleep; fasting; meals; eating; snacks; energy intake; food; nutrition therapy

Small, frequent meals (SFMs) are a dietary regimen characterized by multiple small eating episodes throughout the day that deviate from the common 3-meals-per-day eating regimen presumed to have been adopted by humans for social and practical convenience.[1] Several clinical nutrition guidelines recommend SFMs (eg, 6–10 small meals per day) in the short term for patients who are experiencing early satiety,[2,3] anorexia,[4-12] and gastrointestinal (GI)–related symptoms resulting from disease[8,9,13,14] or pregnancy,[15,16] among several other medical conditions,[17-19] thus making SFMs one of the most commonly used medical nutrition therapies. However, whether the provision of SFMs palliatively improves the morbidity of nutritionally at-risk individuals has yet to be elucidated.

For >40 years, infrequent meal intake has been recognized as a potential risk factor for obesity, hypercholesterolemia, impaired glucose tolerance, and ischemic heart disease.[20-23] Also, a popular recent notion regarding SFMs is that it may lead to increased satiety and improved metabolism, possibly even weight loss. The potential impact on health during the shift from traditional meal regimens (eg, 3 meals per day) to long-term SFMs has thus been examined in healthy individuals in the context of meal frequency,[21,24,25] snacking behavior,[26,27] meal timing,[28-30] and fasting,[1,31,32] providing preliminary evidence that may contradict some of the presumed benefits of SFMs. This narrative review summarizes current clinical guidelines recommending SFMs for the management of diseases in adult patients (≥18 years), with supporting experimental and epidemiologic evidence, and it provides suggestions pertaining to this recommendation by drawing on important considerations from recent related investigations in healthy adults.

Clinical Guidelines for SFM Recommendations

Medical indications for SFMs encompass a range of transient and long-term symptoms observed in patients with a variety of diseases and medical conditions (Table 1). The primary indication for short-term and long-term SFMs is to optimize energy and nutrient intake and ameliorate large meal

From the [1]Department of Nutrition, Brigham and Women's Hospital, Boston, Massachusetts, USA.

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Corresponding Author:
Hassan S. Dashti, PhD, Department of Nutrition, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
Email: hdashti@partners.org

Table 1. Indications for Small, Frequent Meals and the Diseases and Conditions That Warrant Their Recommendation.

Indication	Disease/Condition
Factors influencing energy intake	
Dehydration	Cancer[3]
Dysgeusia	Cancer[3]
Dysphagia	Cancer,[3] elderly[12]
Early satiety	Cancer,[3] gastroparesis[8,9]
Inadequate dietary intake	Cancer,[2,5] chronic pancreatitis,[7] diabetes,[6] dumping syndrome,[10,104] head and neck cancer[2]
Large meal intolerance	Cancer[5]
Optimize caloric intake	Autonomic failure,[18] Hutchinson-Gilford progeria syndrome[11]
Poor appetite	Cancer,[3] head and neck cancer[2]
Gastrointestinal-related factors	
Diarrhea	Head and neck cancer[2]
Gastroesophageal reflex disease	Chronic obstructive pulmonary disease,[105,106] other[107]
Limit meal caloric content and weight	Gastroparesis[8,9]
Mucositis	Oral mucosal diseases (HIV-positive patients)[108]
Nausea	Cancer,[3] pregnancy[15,16]
Prevent slow gastric emptying	Gastroparesis[8,9]
Vomiting	Bariatric surgery,[42] cancer,[3] pregnancy[15,16]
Other factors	
Dumping syndrome	Gastrectomy,[10] other[104]
Dyspnea	Pulmonary fibrosis,[109] chronic obstructive pulmonary disease
Postprandial hypotension	Autonomic failure[18]
Limit nocturnal fasting	Cirrhosis,[34] end-stage renal disease (pretransplant and posttransplant)[17]
Transition to oral diet (posttransplant)	End-stage renal disease (pretransplant and posttransplant)[17]
Tumor growth, depression, pain, treatment side effect	Cancer[3]
Unspecified	Irritable bowel syndrome,[35] short bowel syndrome[110]

intolerance as typically observed in nutritionally at-risk patients with conditions such as cancer, GI complications, or postoperative complications following GI surgery.[4-12] In addition, the indication for SFMs may be specific to certain medical conditions. For example, SFMs may be recommended transiently to avoid dumping syndrome following gastrectomy[10] or to manage dysgeusia, which has been reported in >15% of cancer patients undergoing treatment.[2,33] SFMs may also be a long-term recommendation for cirrhotic patients who are encouraged to focus on 4–7 small meals throughout their waking hours to prevent hypoglycemia that may result from prolonged periods of fasting.[34] Other indications include nausea and vomiting (often postoperatively or resulting from disease or pregnancy).[8,9,13-16] It is important to note that SFMs are often one among several medical nutrition therapies used to manage disease-related symptoms but not treat the disease. In the case of irritable bowel syndrome, for instance, avoiding high-fat foods, dairy, caffeine, and alcohol is encouraged.[35]

Literature Search

To identify studies evaluating the efficacy of SFMs in adult patient populations, a literature search was conducted in the PubMed database for original research, review, and commentary articles published before December 2015. Specific keywords for this search included the following: "small, frequent meals," "meal frequency," or "snacking" and "patients," "disease," "medical nutrition therapy," or "clinical care." We also cross-referenced the citations from recovered studies. Criteria for inclusion were (1) adult patient population (age ≥18 years), (2) randomized controlled trial (RCT) or epidemiologic study comparing at least 2 dietary regimens, and (3) article written in English. Due to the small number of eligible papers, studies of small sample sizes, short duration, and ≤20 years old were included.

Experimental and Epidemiologic Investigations of SFM Efficacy

While patient reports suggest SFM efficacy and tolerance, evidence supporting SFM recommendation for its various indications remains sparse. We identified 3 experimental RCTs and 3 cross-sectional or longitudinal epidemiologic published studies investigating the efficacy of SFMs in diseased populations (Table 2).

Experimental Studies

Few RCTs of limited sample size and duration have evaluated the efficacy of SFMs in improving chronic disease management

Table 2. Experimental and Epidemiologic Studies Investigating Small, Frequent Meals (SFM) Efficacy in Adult Patients.

Population/Medical Condition	Design	SFM or Meal Frequency Definition	Outcome Ascertainment	Key Observations	Recommendation
			Experimental Studies		
31 nutritionally at-risk elderly patients with dysphagia residing in an extended-care health care facility[12]	Randomized crossover study with two 4-d study periods (3 or 5 isocaloric meal regimens)	3 vs 5 meals per day, ~1650-kcal isocaloric dietary regimens.	Total energy and fluid intakes as assessed by individual weighing of amounts served and left after a meal.	Average energy intakes were identical between 3-meal and 5-meal regimens ($P = .565$), but free fluid intake was greater with 5 meals ($P = .003$).	Consider alternative strategies to increase energy intake among this patient population, including high-energy and nutrient-dense foods.
13 free-living men and women with type 2 diabetes or persistently impaired glucose tolerance[38]	Randomized crossover study with two 4-wk periods (regimens of 3 or 9 isocaloric meals)	*3-meal regimen*: breakfast, 25%; lunch, 25%; dinner, ~50%; and a single small snack of ~150 kcal (or 2 small snacks of 75 kcal each). *9-meal regimen*: Each of the 3 meals from the 3-meal eating regimen was divided into 3 smaller meals.	3-d semiquantitative diet record, anthropometrics, seated blood pressure, lipid analysis, glucose, insulin and triglyceride concentrations, creatinine, c-peptide protein, and glycated hemoglobin.	Nutrient intakes and all measures of carbohydrate and lipid metabolism were similar on the 3-meal and 9-meal regimes ($P > .05$). No changes in fasting lipid, insulin, or glucose levels or in glucose, insulin, or triglyceride responses to a glucose load ($P > .05$).	As there were no observed adverse effects of consuming 9 meals per day, it would seem appropriate that meal frequency in those with type 2 diabetes should be left to personal choice, provided that energy balance is maintained.
7 patients with primary chronic autonomic failure[19]	Randomized crossover study with two 1-d periods	3 vs 6 meals per day; isocaloric regimens On the 6-meal regimen, breakfast, lunch, and dinner were split into 2 isocaloric portions.	Daytime ambulatory BP was measured every 30 min between 6 AM and 9 PM with additional recordings while lying, sitting, and standing, 30 min after each meal.	SBP and DBP were lower in all 3 positions after large meals: lying (SBP, $P = .005$; DBP, $P = .02$), sitting (SBP, $P > .05$; DBP, $P = .07$), and standing (SBP, $P > .05$; DBP, $P = .06$). Between meals, BP fell to lower levels with large meals (SBP, $P = .002$; DBP, $P = .0001$). Subjects on 6 meals reported fewer symptoms of dizziness and faintness on sitting and standing following meals, and they were able to stand for a longer period.	Smaller and more frequent meals are recommended, as they may reduce postprandial hypotension and diminish postural symptoms postmeal.
			Epidemiologic Studies		
80 obese females with postoperative Roux-en-Y gastric bypass[42]	Prospective cohort study (followed for 9 mo and assessed every 3 mo)	Diet fractionation (meals per day) was self-reported by patient.	Weight, BMI, 24-h dietary recall, drug consumption, and self-reported vomiting episodes were recorded.	Compared with women who self-reported consuming 3 meals per day, those who self-reported consuming 6 meals per day had higher energy intakes at 3 mo ($P < .05$) and lower weight loss postoperatively at 9 mo ($P < .05$).	Unless indicated to manage vomiting, multiple small meals may not be advantageous following bariatric intervention. For patients with increased vomiting,

(continued)

Table 2. (continued)

Population/Medical Condition	Design	SFM or Meal Frequency Definition	Outcome Ascertainment	Key Observations	Recommendation
				Those consuming frequent meals reported fewer vomiting episodes at 6 mo ($P = .038$).	proper pacing of intake and swallowing small chunks of food with appropriate chewing are necessary.
305 patients with gastroparesis: 204 idiopathic and 101 diabetic[13]	Prospective cohort study	Dietary intake was estimated with the Blood Food Frequency Questionnaire. Meal frequency was estimated with the average sum of vegetable, grain, and meat servings. Estimated meals or servings per day of any food category ≥4 was considered "frequent meals."	Calorie requirements were estimated with the Institute of Medicine dietary reference intakes; calorie-deficient diets were defined as <60% of estimated daily energy requirements; and a deficient intake of specific nutrients was defined as <60% of dietary reference intakes.	Patients consumed on average 1.4 meals per day and 64% of patients were classified as consuming energy-deficient diets (<60% of estimated total energy requirements). Those classified with energy-deficient diets had significantly higher symptom scores for stomach fullness ($P = .005$), excessive fullness after a meal ($P = .005$), bloating ($P = .005$), and constipation ($P = .02$). Those classified with energy-deficient diets consumed fewer meals per day (0.9 vs. 2.2; $P < .001$), and 82.3% consumed <4 meals per day, whereas 50.5% of those consuming adequate diets consumed ≥4 meals per day ($P < .001$).	A low-fat, low-fiber diet of small portions and frequent feedings is recommended to patients with gastroparesis.
4763 Iranian adults with FD[14]	Cross-sectional analysis of the SEPAHAN trial	Meal frequency was assessed by asking participants, "How many main meals do you consume each day?" (1, 2, or 3) and "How many snacks do you consume each day?" (0, 3–5, >5). Total meal frequency was estimated by sum of main meals and snacks per day and grouped into 4 categories: <3, 3–5, 6–7, ≥8.	FD symptoms were assessed with a validated Persian version of the Rome III questionnaire, and FD was defined as bothersome postprandial fullness, early satiation, and/or epigastric pain or epigastric burning. Severity of FD symptoms were evaluated with a 4-item rating scale.	Those who ate 3 meals per day had 52% lower odds of FD vs those consuming 1 meal per day when unadjusted for covariates ($P < .05$). Compared with those who never snacked, individuals who consumed 3–5 snacks had 39%, 42%, and 43% lower odds of FD, postprandial fullness, and epigastric pain, respectively ($P < .05$). Compared with 3 meals and snacks per day, consuming 6 or 7 meals and snacks per day was associated with lower odds of FD, early satiation, and postprandial fullness among women ($P < .05$).	Increasing meal and snack frequency might help prevent FD and its related symptoms.

BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; FD, functional dyspepsia; SBP, systolic blood pressure.

and alleviating related symptoms. Taylor et al investigated the influence of 4 days of either of 2 isocaloric dietary regimens (3 or 5 meals per day providing ~1650 kcal) on intake in 31 nutritionally at-risk elderly patients (mean age = 85 years) with dysphagia residing in an extended care facility. The crossover study yielded no difference in energy intake between the 2 intake regimens.[12] The dietary regimen of 5 meals per day did, however, improve free fluid intake. Whether SFMs may promote higher energy intake in patients with dysphagia as a result of other diseases, such as cancer, remains unknown.

Two early reports in adults with type 2 diabetes comparing the effects of 1 day of few large meals with 1 day of several small meals observed various benefits of frequent meals, particularly lower insulin and glucose levels, lower urinary C peptide excretion, and lower average free fatty acids.[36,37] These studies were followed up by a larger crossover study of 13 patients with type 2 diabetes or persistently impaired glucose tolerance who were randomized to either 3-meal or 9-meal regimens, with each regimen followed for 4 weeks.[38] There were no differences in nutrient intake or changes in fasting lipid, insulin, or glucose levels or in their responses to a glucose load.[38] Based on the weak evidence for frequent meals for adults with type 2 diabetes, the latest national dietary guidelines for individuals with diabetes mellitus offer no comment regarding meal frequency.[39-41]

In another randomized crossover study, 7 patients with chronic autonomic failure who were at risk for a rapid drop in supine blood pressure (BP) and postural hypotension were randomized to a regimen of either 3 large or 6 small meals for 1 day each, to examine differences in daytime BP profiles and BP responses to postural change following meal ingestion.[19] Compared with 6 small meals, the 3 large meals resulted in significantly lower postprandial systolic and diastolic BP when lying and lower intermeal BP. Although not tested for statistical significance, subjects on the regimen of 6 small meals also reported fewer symptoms of dizziness and faintness on sitting and standing following meals, and they were able to stand for a longer period. Accordingly, smaller and more frequent meals were recommended to these patients, as this dietary regimen may reduce postprandial hypotension and diminish postprandial postural symptoms.

In summary, the described trials provide preliminary evidence of benefits accrued from consuming small and frequent meals to treat the symptoms of various chronic illnesses, particularly increasing the fluid intake of elderly patients with dysphagia and decreasing the likelihood of postprandial hypotension in patients with chronic autonomic failure. However, based on the limited sample size (n = 7–31), short duration (1 day to 4 weeks), and specific patient populations (eg, elderly with dysphagia, individuals with diabetes mellitus, and patients with chronic autonomic failure) of these RCTs, the generalizability of these findings remains questionable. In addition, trials supporting transient, short-term recommendations for SFMs (eg, for postoperative patients) are still lacking.

Epidemiologic Studies

Similar to RCTs, few epidemiologic studies have been conducted to investigate the influence of SFMs or frequent meals on improved health outcomes in different patient populations.

Ribeiro and colleagues identified 80 obese women with narrowed gastric outlet after Roux-en-Y gastric bypass (RYGB) who were at risk for protein-calorie malnutrition and Wernicke's encephalopathy.[42] In that prospective cohort study, the relationship between meal frequency and weight loss/vomiting was evaluated at 3-month intervals for a total of 9 months after RYGB. The study observed that, when compared with women who self-reported consuming 3 meals per day, those who self-reported consuming 6 meals per day had higher energy intakes at 3 months and lower weight loss postoperatively at 9 months. However, those self-reporting more frequent meals also cited fewer vomiting episodes at 6 months,[42] suggesting that frequent meals may be an appropriate coping mechanism for vomiting and abdominal discomfort.[42]

SFMs are also commonly recommended to nutritionally at-risk patients with gastroparesis to prevent large meal volumes that may slow gastric empting and result in early satiety.[8,9] An observational study of 305 prospectively enrolled patients with diabetic or idiopathic gastroparesis observed that these patients consumed on average 1.4 meals per day.[13] The study observed that 64% of the patients were consuming energy-deficient diets meeting <60% of their estimated total energy requirements with suboptimal intakes of vitamins and minerals. Those patients classified as consuming an energy-deficient diet were more likely to be consuming fewer meals per day, and only 7.7% of them consumed ≥4 meals per day.[13] Those patients also had significantly higher symptom scores for stomach fullness, excessive fullness after a meal, bloating, and constipation. The low prevalence of frequent meal intake may be due to difficulty in implementation, a lack of consensus regarding this recommendation, or possible delayed gastric emptying with short-term increases in feeding frequency.[43]

Another GI complication that may respond to SFMs is functional dyspepsia (FD), which is characterized by upper GI symptoms including epigastric pain, discomfort, fullness, bloating, nausea, belching, and vomiting as a result of food ingestion. These complications in patients with FD tend to lead to low meal frequency[44,45] and smaller meals.[46] Frequent intake is hypothesized to limit delayed gastric emptying associated with large meals, avoid impaired proximal gastric accommodation, and overcome abnormal secretions of gastric acid and gut hormones.[47,48] A cross-sectional investigation of the SEPAHAN study (conducted in Isfahan, Iran) aimed to unravel whether increased meal frequency assists in managing symptoms of FD.[14] The study observed that those who ate 3 meals per day had 52% lower odds of FD versus those consuming 1 meal per day, when unadjusted for covariates. Compared with those who never snack, individuals who consumed 3–5 snacks had 39%, 42%, and 43% lower odds of FD, postprandial

fullness, and epigastric pain, respectively. Finally, consuming 6–7 meals and snacks per day was associated with lower odds of FD, early satiation, and postprandial fullness when compared with 3 meals and snacks per day among women. These findings suggest that the redistribution of calories through increasing meal and snack frequency may help prevent FD and related symptoms.

In summary, as compared with experimental studies, larger epidemiologic investigations of various patient populations have observed additional benefits with SFM intake. These studies suggest that SFMs may reduce GI symptoms resulting from disease, including vomiting, bloating, and fullness; however, SFMs may not be advantageous from a weight loss standpoint, particularly following bariatric intervention, as it may promote higher energy intakes.

SFM Recommendations for Healthy Individuals and SFM Trends in the United States

Early findings reporting low meal frequency as a risk factor for obesity and cardiovascular disease has generated an interest in following this meal regimen long term for overall health.[20-23] Also, recent anecdotal reports regarding SFMs suggest that it may lead to increased satiety and improved metabolism, potentially even weight loss. Consequently, various weight loss diets may promote SFMs, but this is not yet evident consistently in national nutrition guidelines targeting healthy people. The National Heart, Lung, and Blood Institute suggests SFMs to reduce caloric intake[49]; meanwhile, the 2015 dietary guidelines for Americans lack guidance on meal frequency and distribution, instead acknowledging that US adults consume on average 3 meals per day plus >1 snack (40%–50%, 2–3 snacks; 30%, ≥4 snacks).[50] Another dietary guideline suggests a temporal distribution of energy intake consistent with societal norm: >3 main meals and 1–3 snacks per day.[51]

Despite the lack of SFM recommendation to the general public, secular trends from US national surveys suggest shifts in intake patterns consistent with increased prevalence in an SFM dietary regimen. Over a 40-year span from 1971–1974 to 2009–2010, data from the National Health and Nutrition Examination Survey (NHANES) observed slightly higher intake frequency, along with a 3% shift in percentage of energy from main meals to snacks, which contributes approximately 23% of energy per day in 2009–2010.[52,53] The increase in meal frequency and snacking coincides with shorter intervals between meals and snacks. Also notable was an increase in reports of 2 similarly classified meals (eg, 2 breakfasts) consumed >15 minutes apart. Although consistent with characteristics of SFM dietary regimen, whether these changes reflect true shifts toward SFMs cannot be ascertained through current "meal" definitions. Similar snacking trends and more frequent intake throughout the day were also observed in other populations, particularly among vulnerable populations, including smokers and those of lower education and income levels.[54] Investigations of the health implications of different meal and snack frequencies in healthy populations may have implications for diseased and nutritionally at-risk patients.

Considerations for SFM Recommendation and Potential Contraindications

Multiple important considerations should be accounted for when recommending SFMs, particularly long term, as suggested by studies of healthy populations (Table 3).

Energy Balance

Although the anecdotal notion that SFMs reduce appetite appears consistent with first reports of the association between frequent meal intake and lower body weight,[21] it is not supported by recent experimental and epidemiologic evidence from healthy adults. A randomized crossover trial in 12 healthy adults who completed 2 isocaloric 3-week intervention phases of 3 or 8 meals per day found that, at higher meal frequencies, participants reported significantly stronger hunger and desire to eat. Those with higher meal frequencies also tended toward feeling less full despite equal energy intakes with those of lower meal frequencies. This suggests that intake of fewer, larger meals may better suppress appetite in healthy individuals.[24] Another weight loss trial observed no changes in appetite parameters, peptide YY concentrations, and ghrelin levels in relation to meal frequency during weight loss.[55] In addition, intermeal intake in the form of snacks appears to have poor satiating efficiency irrespective of its macronutrient composition.[56,57]

The relationships between meal frequency and energy intake and weight have been investigated in national surveys and population-based observational studies of healthy adults and have also yielded inconsistent findings. A meta-analysis of 15 studies observed beneficial effects of frequent intake and body composition consistent with first reports of this finding[21]; however, these results were found to be primarily driven by a single study, casting doubt on this relationship.[25] Yet, cross-sectional analyses of the NHANES suggest that higher frequencies of eating, meals, and snacking increased likelihood of overweight/obesity and central obesity in US adults.[58] Weight loss trials observed similar weight loss irrespective of meal frequency[55,59] but favorable influences of frequent meals on fat-free mass with no effect on other markers of health, including glucose, insulin, and lipid metabolism.[59]

Within the past few decades, energy-dense snacks typically high in refined sugar, grains, and saturated fats have permeated the food supply. Increasing meal frequency through convenient snacking, which is estimated to provide 100–300 kcal per snack,[60] may lead to positive energy balance and hinder weight loss.[26] However, a 1-year trial found similar weight loss between individuals randomized to a control group (3 meals

Table 3. Considerations and Corresponding Recommendations for Small, Frequent Meals (SFM) Indication.

Consideration	Recommendation
Positive energy balance	Be explicit in the reason for indicating SFMs, such as desired weight gain for at-risk or malnourished patients, including signs and symptoms to monitor, to enable patients to evaluate self-compliance and effectiveness and to determine appropriate times to transition back to standard eating patterns. Provide an estimate of the length of period—such as short term or transient (<3 mo; eg, postsurgery) vs long term (≥3 mo; eg, dysphagia). Specify the number of small meals (eg, 4–6) and/or an estimated caloric content of each meal (eg, 200–300 kcal). Note: Transitioning back to normal eating patterns is less crucial in older adults, as multiple meals may facilitate adequate intake of nutrients in older adults.
Low dietary quality primarily from snacking, nutrient deficiencies	Educate on healthy eating adhering to the 2015 dietary guidelines or disease-specific dietary guidelines, and focus on a variety of fiber, whole grains, and protein; also choose nutrient-dense whole fruits and vegetables as snacks, as appropriate, particularly for those on long-term SFMs, to obtain adequate intake of all nutrients and deter deficiencies.
Fasting, circadian disruption, inappropriate timing of intake	If fasting is to be avoided, as in patients with cirrhosis, specify meal frequency (eg, every 2 h between 8 AM and 8 PM) and nighttime eating, including its relation to sleep timing.
Disordered sleep	Emphasize sleep hygiene, particularly meals consumed closest to sleep timing, and the need for adequate sleep durations to achieve healthful dietary intakes.
Disordered eating behavior	Evaluate a patient's risk for developing disordered eating behavior (eg, binge eating or irregular eating patterns) through a diet history. Professional support may be warranted to maintain ordered and appropriate intake for patients at risk for disordered eating behaviors.
Personal preference, lifestyle, and medication regimen	Consider the patient's personal preference and lifestyle, including physical activity, work schedule, and living situation, to determine appropriate meal pattern. Assess living situation, particularly in older adults, as implementation of SFMs may pose challenges related to multiple food preparations and feedings, especially when administered within health care facilities. Note: For patients with diabetes or other diseases dependent on long-term medication regimens, if current eating patterns do not appear to be disordered, SFMs may be left for personal choice with necessary adjustments to timing and dosing of medication. Note: For individuals with diabetes mellitus, frequent blood glucose monitoring and use of rapid-acting insulin may be necessary with SFMs.

per day) and an intervention group consuming 3 meals and 3 snacks per day.[27] These findings appear contrary to studies suggesting the weak satiety effects of snacks[56] and to another cross-sectional analysis of NHANES data suggesting that frequent snacking is associated with higher body mass index (BMI).[61] Although the positive association between snacking and positive energy balance is considered unfavorable in the general population, it may be necessary in populations with suboptimal intakes. For example, a study observed that among 297 malnourished hospital patients who received 2 intermeal snacks, energy intake increased by 600 kcal/d and protein intake by 12 g/d; these patients also had a shorter hospital length of stay.[62] In addition, findings in nutritionally at-risk older adults observed that snacking contributes to positive energy balance, including higher intakes of carbohydrate, fat, and protein[63] and improved gait function.[64]

In summary, investigations of the relationship between meal frequency and snacking on appetite, energy intake, and anthropometrics have been inconsistent. Whereas meal frequency and snacking appear to have a limited effect on appetite and weight loss success, they may promote positive energy intakes and higher BMI in healthy adults, particularly older adults. Whether these results—most of which are epidemiologic in design and conducted among healthy adults—are translatable to patients who are generally advised to increase meal frequency for the purpose of achieving positive energy balance requires further investigation.

Meal Quality

Encouraging SFMs may inadvertently promote the intake of unhealthy snacks, contributing primarily fat (saturated fats) and simple carbohydrates (added sugars) and lowering the overall nutrition quality of the diet.[50,65] In the United States, studies have observed major shifts toward an increased intake of convenient salty snacks, chips, and nuts.[52,53] However, other results from the

United States[66] and elsewhere[54] found that frequent intake was also associated with improved dietary quality. Among older adults in particular, snacking was found to contribute to daily intakes of vitamins A, C, and E and beta-carotene[67] and to overall diet quality.[68] Interestingly, these findings are in line with a large body of literature that associates breakfast consumption with beneficial nutrient intake, whereby breakfast skippers consuming fewer main meals have diets of lower quality. Thus, SFMs may provide opportunities to increase intake of healthful foods, especially those not commonly consumed in abundance.

Circadian Disruption and Timing of Meal Intake

The human circadian system is the body's endogenous clock that governs numerous aspects of human physiology and behavior[69]—including the sleep/wake cycle, hormone and neurotransmitter secretion, and cognition—by generating coordinated circadian outputs that regulate what termed *circadian rhythms*. The central circadian clock is located in the superchiasmatic nuclei of the anterior hypothalamus, and similar clocks have been recently identified in peripheral tissues, such as the liver, intestine, and adipose tissue.[70] Notably in the liver, up to 80% of hepatic genes demonstrate circadian rhythmicity. Indeed, during the day, the liver expresses enzymes involved in glycogen synthesis and, during the night, enzymes involved in gluconeogenesis and glycogenolysis to maintain nocturnal blood glucose. Although the circadian clock is an endogenous, autonomous, and self-sustained system, photic and nonphotic environmental cues, including nutrients, can influence the rhythmicity of this system.[70] Circadian disruption, more generally termed *chronodisruption*, may be induced by the effects of aging or disruptive synchronizers, such as inappropriate meal times, and may lead to aberrations in metabolism, producing symptoms such as obesity, insulin resistance, and other adverse health effects as well as GI symptoms (abdominal bloating and pain, constipation, and diarrhea).[71,72] Accordingly, the temporal redistribution of food intake correlates strongly with increased incidence of dyslipidemia, hypertension, and a heightened prevalence of metabolic syndrome among shift workers.[73]

Because of the role of the circadian system in regulating enzymes involved in metabolism, the timing of food intake is critical to ensure circadian alignment and promote overall health, such as proper glycemic control and reduced inflammation.[74] Preliminary evidence suggests that meals earlier in the day tend to better align with the biological clock, while late intake may facilitate higher BMI.[28,29] A study by Garaulet et al observed among overweight and obese individuals on a 20-week weight loss intervention that late eaters (lunch after 3 PM) are less successful at weight loss than early eaters (lunch before 3 PM), independent of 24-hour caloric intake, suggesting that timing of food intake is an independent predictor of weight loss.[30] Additional investigations provide further evidence for the role of the timing of food intake on weight loss success after bariatric surgery, glucose tolerance, and metabolic health. Such timing may be related to differences in hormonal profiles, expression of key metabolic genes, and functionality of organs involved in digestion and absorption, which is optimized for glucose and amino acids during the daytime.[74,75]

Interestingly, it is customary for patients who are receiving long-term nutrition support therapy—whether enteral nutrition or parenteral nutrition (PN)—to be fed primarily for 12-hour periods overnight, generally for convenience purposes (ie, easy mobility during the day). However, preliminary research supports the need for nutrition support therapy to be given during the daytime, as it may promote the integrity of the liver and better mimic "real" intermittent and noncontinuous eating patterns.[72] Limited research comparing 12-hour overnight PN with 3 meals consumed orally found significant shifts in the rhythmicity of triglycerides and free fatty acids in patients receiving PN.[76] Animal studies suggest that PN may alter the circadian rhythms of both the central and peripheral clocks.[72] Thus, whether SFMs promote intakes later on in the day as a result of the redistribution of calories that may be incompatible with biological rhythms, similar to overnight nutrition support, requires further investigation.

Sleep

The influence of dietary intake on sleep has recently been investigated in humans, suggesting that meals—daytime and those closest to bedtime—may influence various sleep parameters.[77,78] An RCT observed that the intake of low fiber and high saturated fat and sugar led to lighter, less restorative sleep with more arousals.[79] Another clinical trial observed that administering a carbohydrate-based meal with a high glycemic index 4 hours before bedtime shortened sleep onset latency in healthy sleepers relative to a low glycemic index meal.[80,81] Other studies further report that higher carbohydrate intake is associated with less fragmented sleep[82-86] and that nighttime intake of certain fruits—such as kiwifruit and tart cherries, which tend to be high carbohydrate foods—also promote sleep.[87-89] One potential mechanism for these links is through brain-based tryptophan, a precursor for the sleep-inducing agent serotonin[83,90]; however, the exact mechanism remains unclear.

As SFMs promote more frequent intakes and possibly nighttime meals closer to bedtime, this dietary pattern may have an impact on various aspects of sleep. Indeed, sleep guidelines from the National Sleep Foundation recommend limiting food intake 2–3 hours before bedtime.[91] As sleep disturbances, particularly short sleep duration, have been associated with various cardiometabolic abnormalities, including hypertension, type 2 diabetes, and cardiovascular disease, it is plausible that SFMs may indirectly affect the risk for various cardiometabolic disease.[92]

Furthermore, epidemiologic evidence suggests that sleep may also have an impact on dietary intake. Cross-sectional

studies have consistently observed associations between short sleep durations of roughly <6 hours per day and higher total energy and total fat intakes, as well as lower intakes of fruits.[92] In addition, short sleep duration may be conducive to irregular eating behaviors deviating from the traditional 3 meals per day, including SFMs and intakes of highly palatable nighttime snacks between 10 PM and 5 AM (after dinner and before breakfast) due to altered hours of wakefulness.[92]

Fasting

Intermittent fasting has been investigated to confer various health benefits, including improved body composition, weight loss, and clinical health biomarkers.[31] Accordingly, maintaining nocturnal or overnight fasting and alternate-day fasting has been encouraged.[1] In addition, nocturnal fasting may be recommended to restrict nighttime eating, which contributes to positive energy balance and lower resting energy expenditure.[32] Increasing meal frequency when following SFM dietary regimens may limit the benefits of intermittent fasting if it curtails the hours of fasting; however, this has yet to be shown.[93]

Despite the health benefits of intermittent fasting, it may be unwarranted for certain patients—especially those with various glycogen storage diseases, suboptimal functional glycogen reserves, and reduced glycogenesis in the liver and muscle.[94] For example, patients with liver cirrhosis exhibit abnormal metabolism, including increased fat oxidations and decreased glucose oxidation.[94] To avoid hepatic glycogen depletion and early-onset breakdown of endogenous protein for gluconeogenesis necessary to maintain normal blood glucose levels, these patients are advised to adopt meal patterns similar to SFMs by supplementing their diets with a carbohydrate-based late-evening snack.

Other

Other considerations of varying importance may be necessary when recommending SFMs. Frequent intake may trigger disordered eating behaviors, such as binge eating (characterized by frequent episodes of eating) or night eating syndrome (with excessive nocturnal intake).[95] Frequent intake may also facilitate irregular intake (ie, daily variation in intake frequency), which has been found to contribute to higher energy intake, reduced insulin sensitivity, and higher serum low-density lipoprotein concentrations.[96,97] Whether SFM dietary regimens mediate eating disorders and irregular eating schedules has not been elucidated.

A possible relationship between eating frequency and colorectal cancer (CRC)—the third-leading cause of cancer death in the United States—has been investigated extensively in case-control and prospective cohort studies with contradictory findings. A meta-analysis evaluating the relationship between eating frequency and risk of CRC provided evidence of an increased risk of CRC with meal frequencies >3 meals per day.[98] However, as these studies are subject to recall bias and as CRC diagnoses may result in changes in usual intakes, this relationship was further evaluated in prospective cohort studies. One such study found no overall association between eating frequency (total meals and snacks) and risk of CRC; however, higher eating frequency was inversely associated with lower risk for CRC in participants with diets of higher quality (as assessed by a higher Dietary Approach to Stop Hypertension, or DASH, score) and among those with predicted high insulin sensitivity.[99] Another prospective cohort study observed an inverse association with CRC risk whereby eating ≥4 times per day was associated with a 28%–38% reduction in CRC risk when compared with eating <3 times per day. However, this finding was no longer significant in multivariable adjusted models.[100] While findings appear contradictory, the investigations of meal frequency on CRC provide further emphasis of the importance of meal quality.

Current Limitations and Future Studies

Evaluations of the efficacy of SFMs are scarce, particularly in improving disease management and alleviating symptoms, and several shortcomings in the existing research need to be taken into account moving forward. A standard definition for SFM factoring in size (ie, caloric content) and frequency is currently lacking. For example, experimental studies have used different meal frequencies when examining the benefits of frequent meals, including regimens of 5, 9, and 13 meals.[12,19,38] Whereas epidemiologic examinations have used a range of definitions to estimate meal frequency, such as combining the number of episodes per day (meal and snack eating) and further separating types of eating occasions (meals vs snacks).[13,14,42] In these studies, frequencies >4 meals per day have typically been used to categorize individuals as "frequent eaters" and are often compared with ≤3 meals per day as the reference group. These epidemiologic studies of large population-based cohorts often utilize dietary assessment tools that have not been designed or validated for the purpose of capturing meal size and frequency; thus, they intrinsically suffer from various biases, such as random misclassification and underreporting of intake. For example, food-frequency questionnaires are designed to estimate habitual caloric intake by asking the respondent to classify serving sizes as small, medium, or large in reference to a specified listed serving size and are not designed to parse out meals from snacks. In dealing with these limitations, several assumptions pertaining to meal patterns are often made, such as categorizing foods of low dietary quality, including chips, cookies, and pastries, as snacks by default. In addition, questions such as "On average, how many times a day did you eat (meals plus snacks)?" and questions on the times of usual intake have been used to supplement data collected from food-frequency questionnaires.[99]

Contributing to the absence of a single definition for SFMs is the wide variety of meal regimens that may qualify as "small" and "frequent." However, a definition would be crucial for

proper interpretation of SFM efficacy and for the purpose of meaningful comparisons among studies. Thus, determining a meal size in calories, volume, or dietary composition that qualifies as "small" along with a dietary assessment tool that appropriately estimates size and frequency is necessary moving forward. Reports of duplicate meals (eg, 2 breakfasts) and fewer reports of 3 main meals (~60% in the 2009–2010 NHANES), in addition to changes in meals in terms of size and content—suggest the evolution of meal patterns such that traditional questionnaires requiring surveyors to classify meals as "breakfast," "lunch," "dinner," or "snack" and to limit counts to 1–8 meals per day[99] may hinder the proper capture of modern-day dietary patterns.[52,53] This is particularly the case when evaluating the dietary intake of shift workers with uncommon dietary patterns and unusual timings of intake. Therefore, in epidemiologic studies, open-ended documentation of dietary intake through food diaries and records, meal pattern questionnaires,[101] or mobile technologies may be necessary for this purpose. Furthermore, food diaries and records enable the collection of information beyond traditional dietary tools, including meal timing. A recently developed meal pattern questionnaire was designed to capture main, light, and snack meals and timing without much burden from respondents.[101] Also, documenting intake through the use of real-time mobile technology may be appropriate for modern time. Through the use of a mobile application, an investigation was effectively able to monitor hours of eating duration and complex eating patterns over an extended period in healthy adults.[102] Likewise, investigations using smartphone applications are currently underway to determine factors contributing to weight regain following bariatric surgery in adults, including meal frequency (registered at projectreporter.nih.gov as 1R01DK108579-01).

As it remains unclear whether 3 meals per day or SFMs are optimal, future RCTs and epidemiologic studies of larger sample sizes are essential to formulate appropriate strategies for the management of diseases and disease-related symptoms. In addition, as SFMs are recommended in (1) the short term as a transient meal regimen indicated postoperatively or while disease symptoms last and (2) the long term for the management of symptoms of chronic illnesses, future trials should investigate the effects of short-term and long-term SFMs on patients' health by comparing multiple isocaloric and isonitrogenous eating patterns among patients with acute or chronic disease symptoms. However, longitudinal studies may be appropriate in examining the longer-term benefits of SFMs in the management of patients with chronic disease. In addition, it is imperative for future studies to assess for effect modification by meal quality and BMI and to further consider sleep as a factor influencing dietary patterns.

Recommendations

Consuming SFMs may be necessary for the overall health and well-being of patients during acute and chronic illness. As SFMs may also result in unwarranted weight gain, suboptimal nutrition quality, later meal times, sleep disturbances, limited intermittent fasting, and disordered eating (eg, binge-eating behavior and irregular eating patterns), it is prudent for health professionals to supplement SFM recommendations with additional instructions to avert unwanted consequences (Table 3). Thus, nutrition professionals should be explicit in their reason for indicating SFMs, such as desired weight gain for at-risk or malnourished patients. Additional information to offer patients includes the signs and symptoms to monitor, (1) to enable them to evaluate self-compliance and effectiveness and (2) to determine the appropriate times to transition back to standard eating patterns, if SFMs are recommended only transiently. Providing an estimated length of time to follow the diet is necessary, whenever possible—whether short term (<3 months; eg, post-surgery) or long term (≥3 months; eg, dysphagia). Transitioning back to normal eating patterns is less crucial in older adults, as multiple meals may facilitate adequate intake of essential nutrients.[63] Specifying the number of meals (eg, 4–6 small meals) and/or an estimated caloric content of each meal (eg, 200–300 kcal per meal) may help achieve desirable energy goals (positive, negative, or neutral energy balance) and prevent undesirable energy intakes that may exacerbate underlying diseases, such as excess intake leading to weight gain in patients with cirrhosis.

In addition to meal distribution, another avenue to prevent inappropriate diets is to promote healthy eating adhering to the 2015 dietary guidelines or disease-specific dietary guidelines and focusing on a variety of foods rich in whole grains, fiber, and protein—as well as nutrient-dense whole fruits and vegetables as snacks, as appropriate—to ensure adequate intake of all nutrients and to deter deficiencies, particularly for those following long-term SFM eating patterns.[50] Focusing on increasing healthy meal variety may also be an effective strategy to raise total energy intake, especially for those with poor appetite.[103]

If fasting is to be avoided, meal timing and frequency (eg, every 2 hours between 8 AM and 8 PM) should be further discussed, as well as nighttime eating, including its relation to sleep timing. Furthermore, sleep hygiene should be emphasized, especially meals consumed closest to sleep timing, and the need for adequate sleep durations to achieve healthful dietary intakes. Evaluating a patient's risk for developing disordered eating behavior (eg, binge-eating disorder or irregular eating patterns) or becoming susceptible to an all-day-grazing routine due to social or psychological reasons may preclude recommending SFMs; instead, other support may be integral to maintain ordered and appropriate intake for those patients.

Self-preference and lifestyle (eg, physical activity, work schedule, living conditions) should further be considered. If current eating patterns do not appear to be disordered, particularly for patients with diabetes or other diseases dependent on long-term medication regimens, SFMs may be left for personal choice with necessary adjustments, such as frequent blood glucose monitoring and timing and dosing of

medication. Also, as implementation of SFMs may pose challenges related to multiple food preparations and feedings—specifically when administered within health care facilities where individuals may be group fed—assessment of lifestyle, with an emphasis in older adults, is further warranted. It may thus be important to consider alternative long-term strategies to increase intake, including meal fortification and oral nutrition supplementation, which may be more effective at enhancing total energy intakes.[4]

Conclusions

Three meals per day plus multiple snacks have become the norm in the past half century; however, this common dietary regimen may not be well tolerated by patients.[50] Guidelines and reports have suggested that frequent intakes of small meals are necessary for patients with various diseases and symptoms—most commonly, inadequate dietary intake and GI-related symptoms, such as nausea and vomiting. Limited evidence suggests that SFMs may promote higher energy and fluid intakes, reduce GI discomfort and symptoms (including vomiting, bloating, and fullness), and prevent postprandial hypotension in patients with primary autonomic failure. The sparse evidence supporting SFMs does not necessarily preclude its recommendation; instead, following a regimen of SFMs may be left for the patient to choose. However, several considerations need to be accounted for in recommending SFMs, including their influence on energy balance, meal quality, later meal times, sleep, fasting, and disordered eating. Accordingly, to deter potential health complications that may exacerbate the underlying disease or related symptoms in patients, it may be necessary for SFM recommendations to provide guidance on meal size, frequency, and timing, along with a strong emphasis on healthy meal quality, sleep hygiene, and healthy eating habits. Also, there is an urgent need to further evaluate the efficacy of short-term and long-term SFMs in improving disease management and alleviating symptoms. Future research should address several current shortcomings, including the lack of a standard definition for SFMs, and it should utilize better methods to obtain reliable data on meal patterns, including open-ended questionnaires, meal pattern questionnaires, and mobile technologies.

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Statement of Authorship

H. S. Dashti and K. M. Mogensen equally contributed to the conception and design of the research; and H. S. Dashti contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Burden and Outcome of Vitamin D Deficiency Among Critically Ill Patients: A Prospective Study

Enas Anwar, MD[1]; Gehan Hamdy, MD[2]; Eman Taher, MD[3]; Esmat Fawzy, MD[4]; Sherif Abdulattif, MD[5]; and Mohamed H. Attia, MD[6]

Abstract

Background: Vitamin D deficiency is a prevalent condition among critically ill patients. Information about the relationship between vitamin D levels and outcomes in the intensive care unit (ICU) is sparse. *Purpose:* To evaluate vitamin D status among critically ill patients and its relevance to severity of illness, ICU stay period, and mortality. *Methods:* This prospective multicenter study was conducted in the ICUs of Fayoum, Cairo, Alazhar, and Ain Shams university hospitals. All patients were subjected to interview questionnaire, laboratory investigation, vitamin D level assessment, and severity of illness evaluation using the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score. *Results:* In total, 250 patients were included in the study. The median age was 62 (40–73) years, and most patients were male (52%). The median serum level of vitamin D was 19 (7–40.6). Vitamin D was deficient in 197 patients (78.8%) on admission. While we grouped the ICU patients as vitamin D deficient, insufficient, and sufficient, vitamin D–deficient patients had more severe diseases (mean APACHE II score, 44 ± 15; $P = .014$). Prolonged ICU stay was observed among the deficient group but with no significant association. The overall mortality rate was 6.8%; of these, 70.5% were vitamin D–deficient patients. However, logistic regression analysis demonstrated that vitamin D deficiency was not an independent risk factor for mortality. *Conclusion:* Vitamin D insufficiency is common in critically ill patients (69%); it is associated with more severity of illness, but it is not an independent risk factor for longer ICU stay or mortality. (*Nutr Clin Pract*.2017;32:378-384)

Keywords

vitamin D; mortality; hospital stay period; critically ill patients; vitamin D deficiency; critical illness; length of stay; intensive care units

Vitamin D is a fat-soluble vitamin that is converted in the body into biologically active metabolites, 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D. These metabolites regulate numerous functions in a variety of cell types. The key role played by vitamin D together with calcium in bone health is well known.[1]

Since receptors for vitamin D have been discovered all over the body, the Endocrine Society recommended a serum 25(OH)D concentration of at least 30 ng/mL for optimal health benefits.[2] The vital role of vitamin D in the immune system has been recognized through its receptors, which are present in different immune cells, including activated CD4 and CD8 T cells, B cells, neutrophils, macrophages, and dendritic cells, as well as its role in regulating immunoglobulin production.[3] Vitamin D has been shown to have anti-inflammatory and antiproliferative properties, and its deficiency has been linked to mortality.[4]

Although the role of vitamin D in the prevention and control of skeletal disorders was established a long time ago, its association with nonskeletal chronic diseases became evident in the 2000s.[5] Those diseases include certain types of cancer, diabetes, cardiovascular diseases, hypertension, and metabolic syndrome.[6–8]

Different degrees of vitamin D deficiency affect as many as 1 billion people worldwide. This high prevalence of vitamin D deficiency in the general population leads to the concern that this deficiency might be of importance for the critically ill.[2,9]

Vitamin D deficiency is rarely considered or treated in critically ill patients. Also, the prevalence of vitamin D deficiency and its significance in intensive care units (ICUs) are still unknown and not well studied.[1,10]

The prevalence of 25(OH)D deficiency in critically ill patients has been reported to range from 17%–79%.[1,11,12]

From the [1]Internal Medicine Department, Faculty of Medicine, Fayoum University, Fayoum, Egypt; [2]Internal Medicine Departments, Faculty of Medicine, Cairo University, Cairo, Egypt; [3]Community Department, Faculty of Medicine, Cairo University, Cairo, Egypt; [4]Clinical and Chemical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt; [5]Anesthesia & ICU Department, Faculty of Medicine, Alazhar University, Cairo, Egypt; and [6]Internal Medicine Departments, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

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Corresponding Author:
Gehan Hamdy, MD, Faculty of Medicine, Internal Medicine Department, Cairo University, 100 Hay Al Ashgar Compound 6th October City, Cairo, Alahram, Giza, Egypt.
Email: gegehamdy@gmail.com

Vitamin D deficiency and its association with multiple health outcomes have been studied by a large number of observational studies and randomized controlled trials. Great debates exist about the role of the vitamin among critically ill patients, and most studies reported that vitamin D is more likely to be a correlate marker of overall health and not causally involved in diseases.[5]

This study aims at evaluating the prevalence of vitamin D deficiency in ICU patients and correlating its level with patients' outcomes, which include disease severity, duration of ICU stay, and mortality.

Method

Setting and Duration of Work

The study was conducted in ICUs of Fayoum, Cairo, Alazhar, and Ain Shams university hospitals. The work was conducted throughout a 4-month period, from July 2013 through August 2013. It was also done during the same months in 2014 to control for any seasonal variation in the level of vitamin D concentration.

Study Design

A prospective analytical multicenter study was designed in which enrolled patients were followed up from the time of admission to ICU units until the time of occurrence of outcomes (discharge from ICU or death).

Sample Size and Patients

Sample size was calculated using EPICALC 2000 version (setting the prevalence at 80%, precision at 5%, and confidence interval at 95%), which yielded a sample of 245 patients. The study enrolled 250 patients. The only exclusion criterion was the patient being on vitamin D supplementation prior to the current admission. The recruited patients did not receive any vitamin D supplementation during the period of hospitalization.

Data Collection

After taking informed consent from the patients or their relatives, the recruited patients were subjected to a precoded interview questionnaire that included baseline demographic data (age and sex), the reason for admission, clinical assessment data, and laboratory investigation. The length of ICU stay was also recorded. The length of stay was defined as the time from ICU admission until the time of transfer out of the ICU. Although several scoring systems have been developed to grade the severity of illness in critically ill patients, the investigators applied the most commonly used: the second version of the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score introduced in 1985. It generates a point score ranging from 0–71 based on 12 physiologic variables, age, and underlying health. Also, it can calculate estimated mortality for every patient.[13]

Samples for serum total 25(OH)D and intact parathyroid hormone (IPTH) concentrations were withdrawn separately for the study purpose in the first 24 hours of ICU admission.

Samples were collected in plain tubes and covered with foil. After 15 minutes, they were centrifuged. Serum was separated in other tubes, and then all samples were kept in the deep freezer until the time of assay. Assessment of 25(OH)D was carried out by the second-generation platform of electrochemiluminescence (ECL) technology (Cobas 4111; Hitachi-Roche Diagnostics GmbH, Mannheim Germany). IPTH was assayed using the DXI 800 (Beckman Coulter, Brea, CA).

According to the Institute of Medicine, Food and Nutrition Board,[14] patients were classified into 3 groups based on vitamin D concentration as follows:

1. A healthy group with a level of vitamin D concentration >30 ng/mL (75 nmol/L)
2. An insufficiency group with a level of vitamin D concentration of 20–30 ng/mL (50–75 nmol/L)
3. A deficiency group with a level of vitamin D concentration <20 ng/mL (50 nmol/L)

Statistical Analysis

For each numeric variable, the normality of distribution was preliminarily assessed by the Kolmogorov-Smirnov test. Normally distributed variables were generally expressed as mean and standard deviation (SD). Abnormally distributed variables were expressed as median (25th quartile, 75th quartile). All qualitative data were presented as frequency and percentages. The relation of each variable with the outcome categories was separately tested by the χ^2 test for categorical variables, analysis of variance (ANOVA) with the post hoc test, or Mann-Whitney and Kruskal-Wallis tests for continuous variables. Correlation of vitamin D with other variables was tested by the Spearman test. To determine which combination of predictor variables led to the best predictive model, multivariate logistic regression analysis was carried out by using stepwise forward modeling (probability of F to enter = 0.05 and probability of F to remove = 0.10). The length of stay was dichotomized based on its median value (7 days) into 2 categories: short stay (≤7 days) and long stay (>7 days). All P values <.05 were considered significant. Data analysis was conducted using SPSS (version 15; SPSS, Inc, an IBM Company, Chicago, IL).

Ethical Consideration

The study design and method were approved by the Ethical Committee of the Department of Public Health, Cairo University. Data confidentiality was preserved throughout the study in accordance with the revised Helsinki Declaration of Bioethics. All

Table 1. Baseline Characteristics of the Patients Admitted to the Intensive Care Unit (ICU) (n = 250).

Patient Characteristic	Value
Age, median (IQR), y	62 (40–73)
Sex, No. (%)	
Male	130 (52)
Female	120 (48)
Diagnosis at time of hospital admission, No. (%)	
Medical	208 (83.2)
Surgical	42 (16.8)
APACHE II score, mean ± SD	32.9 ± 14.8
Estimated mortality, median (IQR), %	10.6 (4.7–27.1)
Length of ICU stay, median (IQR), d	7.0 (3.0–14)
Outcome, No. (%)	
Discharged	233 (93.2)
Died	17 (6.8)

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; IQR, interquartile range.

Table 2. Distribution of Admitted Patients According to the Main Cause of Admission to the Medical Intensive Care Unit.

Cause of Admission	No. (%)
Myocardial infarction	70 (28.0)
Respiratory failure, pneumonia	33 (13.2)
Diabetic ketoacidosis	25 (10.0)
Sepsis and septic shock	25 (10.0)
Neurological affection (stroke and coma)	20 (8.0)
Gastrointestinal problem (liver disease, bleeding)	18 (7.2)
Other different causes	59 (23.6)

Table 3. Hematological and Biochemical Profile of the Patients Admitted to the Intensive Care Unit.

Laboratory Result	Value
Vitamin D level, median (IQR), ng/mL	7.6 (2.8–16.24)
Creatinine, median (IQR), mg/dL	1.01 (0.7–1.7)
Calcium, mean ± SD, mg/dL	7.6 ± 0.8
Phosphorous, mean ± SD, mg/dL	3.7 ± 1.54
IPTH, mean ± SD, pmol/L	7.88 ± 2.12
WBCs, median (IQR), 10^9/L	11.9 (8.7–17.5)
Corrected calcium, mean ± SD, mg/dL	8.8 ± 0.4

IPTH, intact parathyroid hormone; IQR, interquartile range; WBCs, white blood cells.

patients were informed about the aims of the study. Written informed consents were obtained from the participants or their relatives, who agreed to participate in the study.

Results

Basic Characteristics of the Patients

This prospective study enrolled 250 patients who were admitted to the ICU. Regarding the basic characteristics of the studied patients (Table 1), the age ranged from 18–88 years, and the median was 62 (40–73) years. For men, the median age was 61.5 (44.7–73) years, and for women, it was 63 (39–74.7) years (P = .602). Almost equal distribution of men (52%) and women (48%) was observed. Patients were admitted mainly for medical reasons (83.2%). The severity of score that was assessed by APACHE II ranged from 8–67, with a mean of 32.9 ± 14.8. The estimated mortality ranged from 0.7%–89.4%, with a median value of 10.6 (4.7–27.1). The length of ICU stay ranged from 1–50 days, with a median value of 7 (3–14) days. At the end of the study, 93.2% of the patients were discharged, while 6.8% died. Most patients (83.8%) were admitted for medical causes, and only a few cases were admitted for surgical ones. The main cause of admission is presented in Table 2.

IPTH values ranged from 2.0– 30 pmol/L with a mean of 7.88 ± 2.12 pmol/L (normal range, 1.3–9.3). The value of vitamin D concentration ranged from 2.8–39.12 ng/mL (Table 3).

Comparison of the 3 Groups

Patients were classified into 3 groups based on vitamin D concentration. The deficient group consisted of 197 patients (78.8%) with a median vitamin D level of 4 (2.8–10.2) ng/mL. The sufficient group consisted of 37 patients (14.8%) with a median level of 24.76 (18.28–27.69) ng/mL. The healthy group consisted of 16 patients (6.4%) with a median level of 35.32 (23.67–37.24) ng/mL (Figure 1). Among the deficient group, severe deficiency (vitamin D levels <5 ng/mL) was recorded in 51.2%, moderate deficiency (vitamin D levels 5–10 ng/mL) in 23.3%, and mild deficiency (vitamin D levels 10–20 ng/mL) in 25.5%. Comparison of the 3 groups of patients as shown in Table 4 revealed that the deficient group was significantly younger than the sufficient and healthy group (median age, 57, 66, and 73 years, respectively). Age comparison between each group revealed that the significant change was between the deficient group and the healthy group (P = .003).

No significant difference between groups was detected based on sex.

Vitamin D Concentration and APACHE II Score

The severity of illness was significantly higher among the deficient group, as indicated by the higher score compared with the other 2 groups, with the mean values of 44 ± 15, 33 ± 14.8, and 27 ± 13, respectively. Also, the estimated mortality was significantly higher in the deficient group (Table 4). However, the severity score and estimated mortality failed to show significant correlation with vitamin D concentration (r = 0.05, P = .56 and r = −0.02, P = .71, respectively). Post hoc test was applied

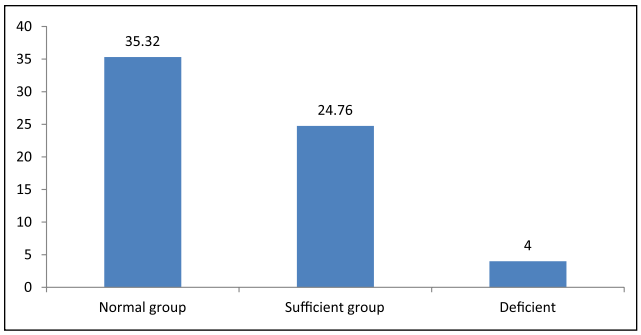

Figure 1. The median level of vitamin D (ng/mL) among the 3 groups of the patients admitted to the intensive care unit.

to demonstrate the significance between each group. It showed that the healthy group was significantly different from the other 2 groups.

Vitamin D and Prolonged ICU Stay

Despite the prolonged stay that was observed among the deficient group, no significant difference was detected (Table 4). The median level of vitamin D was 6.4 (2.8–14.32) ng/mL among patients with a prolonged stay and 8.08 (2.8–20) ng/mL among patients with a short stay ($P = .27$). The results of binary multivariate logistic regression are demonstrated in Table 5. It included age, sex, severity score, vitamin D level, and diagnosis. The significant predictors for long ICU stay length were the severity score and medical diagnosis ($P = .01$ and $P = .02$, respectively). Also, no significant correlation was found between vitamin D concentration and length of hospital stay ($r = -0.08$, $P = .27$).

Vitamin D Concentration and Mortality

The median level of vitamin D among deceased patients was 8 (2.8–29.8) ng/mL, while among the discharged, it was 7.6 (2.8–15.84) ng/mL. Binary multivariate logistic regression was done to detect the significant predictors of outcome. It included age, sex, severity score, and vitamin D concentration. The only significant predictor was the severity score ($P = .02$). This is demonstrated in Table 6. Significant changes were detected between each group and the other 2 groups.

Discussion

Vitamin D is a prohormone important for serum calcium and phosphorus homeostasis, which is crucial for proper neuromuscular function and skeletal health. Vitamin D can be obtained from food or made in skin after exposure to ultraviolet B radiation of the sun, which is the main source of vitamin D, with ample opportunities to form vitamin D during spring, summer, and fall. This study recruited patients during summer months in 2 consecutive years to control for seasonal variation. Vitamin D deficiency is likely to be common in hospitalized patients, especially among the critically ill.[15] Unfortunately, data regarding the relationship between vitamin D concentrations and outcomes of ICU patients are sparse.[16] However, with the rising concerns about the association between vitamin D concentration, inflammation, and sepsis, it was hypothesized that it has a role in the ICU. Thus, we aimed to assess the prevalence of vitamin D deficiency in ICU patients and to correlate its levels with patients' outcomes.

Our study showed that patients with 25(OH)D deficiencies were generally younger than patients with normal 25(OH)D levels and were mainly males. Most published studies show a higher prevalence of vitamin D deficiency in women and the elderly.[17,18] However, the large multicenter study by Braun et al[19] confirmed our association between low 25(OH)D levels and younger age but not with the male sex. Multiple studies have demonstrated that vitamin D deficiency is a common finding among critically ill patients.[20,21] In addition to the well-known risk factors for vitamin D deficiency, including age, living in northern latitudes, dark skin color, obesity, low dietary intake of vitamin D, and various medical conditions, especially malabsorption syndromes, other risks should be considered, especially in ICU-admitted patients, such as fluid resuscitation, gastrointestinal affliction, and interaction with medical treatment.[22]

Our study showed that the prevalence of vitamin D deficiency was 78.8%. This finding is consistent with other studies that reported the prevalence to be 82.3%, 77.8%, and 80.4%.[23–25]

A higher level of vitamin D deficiency (96.1%) was reported by Long-Xiang et al,[26] who interpreted this figure by the fact that their study was conducted in winter, which has been associated traditionally with low vitamin D as the patients were not exposed to sunshine.

The contribution of vitamin D in the severity of illness has been studied. Our results illustrated a significant association between vitamin D deficiency and severity of illness as evaluated by APACHE II score, which may be attributed to the pleiotropic actions of vitamin D in different body functions, including immunity, endothelial and mucosal functions, and metabolic functions.[27,28] Also, the contribution of vitamin D deficiency to multiple-organ failures and occurrence of systemic inflammatory response syndrome play an important role in affecting the severity of illness in critically ill patients.[1] Similar results were deduced by Ginde et al[29] and Zivin et al,[30] while other studies demonstrated no significant association with the severity score, and this may be due to the small sample sizes of both studies, which were 130 and 156 patients, respectively.[23,26]

In the present study, the length of ICU stay was dichotomized into <7 and >7 days. Although a lower level of vitamin D was recorded among patients with a longer stay, the result failed to prove significance. Also, the only significant predictors for a longer stay as shown by the multivariate analysis

Table 4. Comparison of Patients' Demographic and Clinical Data Based on Their Vitamin D Level.

Patient Characteristic	Vitamin D Level			*P* Value
	Deficient (<20 ng/mL) (n = 197; 78.8%)	Insufficient (20–30 ng/mL) (n = 37; 14.8%)	Healthy (30–100 ng/mL) (n = 16; 6.4%)	
Age, median (IQR), y	57 (35–72)	66 (48–75.2)	73 (68–77.3)	.008[a,b]
Sex, No. (%)				
Male	102 (51.7)	22 (59.4)	6 (37.5)	.59[c]
Female	95 (48.3)	15 (40.6)	10 (62.5)	
Diagnosis, No. (%)				
Medical	157 (79.6)	35 (94.6)	16 (100.0)	.06[c]
Surgical	40 (20.4)	2 (5.4)	0 (0.0)	
APACHE II score, mean ± SD	44 ± 15	33 ± 14	27 ± 13	.014[d]
Length of ICU stay, median (IQR), d	7.0 (4.0–14)	5.0 (3.0–12)	5.0 (3.0–11)	.47[a]
Estimated mortality, median (IQR), %	25 (11–49)	11 (4.0–27)	6.0 (4.0–15)	.01[a,e]
Outcome, No. (%)				
Discharged	185 (93.9)	35 (94.6)	13 (81.2)	.21[c]
Died	12 (6.1)	2.0 (5.4)	3.0 (18.8)	

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range.
[a]Kruskal-Wallis *H* test was used.
[b]Significant difference between deficient and normal groups by Mann-Whitney ($P = .0001$).
[c]χ^2 test was used.
[d]Analysis of variance test was used.
[e]Significant difference between deficient and normal groups by Mann-Whitney ($P = .002$).

Table 5. Multivariate Analysis for Predictors of the Intensive Care Unit Length of Stay.

Predictor	Exponential B (CI)	*P* Value
Age	0.99 (0.91–1.0)	.2
Sex	1.4 (0.7–2.8)	.3
APACHE II score	1.03 (1.0–1.06)	.01
Vitamin D deficiency	3.6 (0.8–16.2)	.1
Vitamin D insufficiency	2.4 (0.4–12.5)	.3
Vitamin D normal (reference)		
Diagnosis (medical)	3.4 (1.2–9.5)	.02
Constant	0.03	.007

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II.

Table 6. Multivariate Analysis for Predictors of Mortality.

Predictor	Exponential B (CI)	*P* Value
Age	1.03 (0.99–1.1)	.15
Sex	1.0 (0.3–3.9)	.9
APACHE II score	1.1 (1.0–1.11)	.02
Vitamin D deficiency	0.6 (0.03–8.7)	.7
Vitamin D insufficiency	0.5 (0.08–3.5)	.5
Vitamin D normal (reference)		
Constant	0.001	.007

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II.

were the severity of illness and medical cause for admission. Similar results were mentioned by Venkatram et al[24] and Aygencel et al.[31] On the contrary, McKinney et al[21] reported a significant association between longer ICU stay and low vitamin D level. They dichotomized the length of stay into <3 and >3 days so that 60% of their patients had a hospital stay of fewer than 3 days. Deficiency of 25(OH)D has been implicated in much adverse systematic manifestation such as sepsis, stroke, autoimmune disease, myocardial infarction, heart failure, and other organ failure that may increase mortality.[32–35] The increased mortality might be also due to changes in glucose and calcium metabolism as well as immune and endothelial cell dysfunction.[36] Furthermore, it amplifies the metabolic derangement that is commonly seen in critically ill patients.[37]

A great controversy exists among different studies that assessed the association of vitamin D deficiency and mortality. Some studies suggest an association between vitamin D deficiency and mortality in critically ill patients.[19,24] A recent Cochrane review of 50 randomized trials with 94,148 participants showed that vitamin D in the form of vitamin D3 seems to decrease mortality predominantly in elderly women.[38] The main strength of the study is their large patient population, which improves the reliability of the results. In a study done by Van den Berghe et al,[39] vitamin D levels were lower among nonsurviving critically ill patients. A similar finding was

reported by Lee et al,[1] who revealed a 3-fold rise in mortality rate in vitamin D–insufficient patients compared with those who were sufficient, and by McKinney et al,[21] who revealed vitamin D insufficiency to be nearly twice as prevalent among nonsurvivors in the ICU than among the survivors. Our study exhibited a nonsignificant association and revealed that the only significant predictor of mortality was the severity score. Our finding is consistent with Cecchi et al,[40] who observed that vitamin D levels had no relevance to mortality. Long-Xiang et al[26] also concluded that no there was no difference whether in terms of 28-day survival or 90-day survival between deficient and normal levels of vitamin D, and the only independent risk factor for mortality in their study was APACHE II score. The results of Lucidarme et al[20] confirmed the previous findings. Nair et al[41] conducted a multicenter cohort study to examine the association between vitamin D levels and clinical outcome. They reported that vitamin D deficiency is not associated with increased mortality. The most recent meta-analysis study, conducted by Theodoratou et al,[5] identified 107 systematic literature reviews, 74 meta-analyses of observational studies of plasma vitamin D concentrations, and 87 meta-analyses of randomized controlled trials of vitamin D supplementation and proved that highly convincing evidence of the role of vitamin D and different negative outcomes does not exist.

Limitations of the Study

The overall low mortality rate makes it difficult to detect a difference in mortality in relation to the vitamin concentration. Single measurement of vitamin D did not allow monitoring of changes in vitamin level during the ICU stay. High prevalence of medical vs surgical ICU patients limits the ability to extrapolate the results to all ICU patients.

Conclusion

In our results, vitamin D deficiency is prevalent among critically ill patients admitted to the ICU. The patients were mainly medical ICU patients. Despite the significant association between vitamin D level and severity of illness, no significant association was detected between the level of vitamin D concentration and the length of ICU stay or mortality.

Recommendation

Further studies are recommended with a larger sample size to assess if there is a direct causation between vitamin D status and patient outcomes, especially hospital stay and mortality. Further studies are warranted to clarify whether vitamin D supplementation is beneficial among critically ill patients.

Statement of Authorship

E. Anwar, G. Hamdy, E. Taher, E. Fawzy, S. Abdulattif, and M. H. Attia equally contributed to the conception and design of the research; E. Anwar, G. Hamdy, E. Fawzy, S. Abdulattif, and M. H. Attia contributed to the collection of the data; E. Taher, E. Anwar, E. Fawzy, and S. Abdulattif contributed to the analysis of the data; and G. Hamdy, E. Taher, and M. H. Attia contributed to the interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Treating Dehydration at Home Avoids Healthcare Costs Associated With Emergency Department Visits and Hospital Readmissions for Adult Patients Receiving Home Parenteral Support

Denise Konrad, RD, LD, CNSC[1]; Scott Roberts, MS, RD, LD, LPN[2]; Mandy L. Corrigan, MPH, RD, LD, CNSC, FAND[1,3]; Cindy Hamilton, MS, RD, LD[4]; Ezra Steiger, MD, FACS, FASPEN, AGAF[5]; and Donald F. Kirby, MD, FACP, FACN, FACG, AGAF, CNSC, CPNS[5,6]

Abstract

Background: Administration of home parenteral support (HPS) has proven to be cost-effective over hospital care. Avoiding hospital readmissions became more of a focus for healthcare institutions in 2012 with the implementation of the Affordable Care Act. In 2010, our service developed a protocol to treat dehydration at home for HPS patients by ordering additional intravenous fluids to be kept on hand and to focus patient education on the symptoms of dehydration. *Methods:* A retrospective analysis was completed through a clinical management database to identify HPS patients with dehydration. The hospital finance department and homecare pharmacy were utilized to determine potential cost avoidance. *Results:* In 2009, 64 episodes (77%) of dehydration were successfully treated at home versus 6 emergency department (ED) visits (7.5%) and 13 readmissions (15.5%). In 2010, we successfully treated 170 episodes (84.5%) at home, with 9 episodes (4.5%) requiring ED visits and 22 hospital readmissions (11%). The number of dehydration episodes per patient was significantly higher in 2010 ($P < .001$) and may be attributed to a shift in the patient population, with more patients having malabsorption as the indication for therapy in 2010 ($P = .003$). *Conclusion:* There were more than twice as many episodes of dehydration identified and treated at home in 2010 versus 2009. Our protocol helped educate and provide the resources required to resolve dehydration at home when early signs were recognized. By reducing ED visits and hospital readmissions, healthcare costs were avoided by a factor of 29 when home treatment was successful. (*Nutr Clin Pract*. 2017;32:385-391)

Keywords

dehydration; home parenteral support; home parenteral nutrition; home intravenous fluids; healthcare costs; home care services

Home parenteral support (HPS) encompasses both parenteral nutrition (PN) and intravenous fluids (IVF) and has been a viable therapy for >30 years for patients with intestinal failure from bowel obstruction, dysmotility, surgical resection leading to short bowel syndrome, congenital defect, or impaired absorptive ability. With every home-based treatment, there are associated risks involved. HPS requires intravenous access and therefore can be associated with complications such as catheter-related infections, catheter malposition or dislodgement, and thrombosis. Other short-term metabolic complications include electrolyte abnormalities, glucose imbalances, and dehydration. With long-term use, PN-associated liver disease, metabolic bone disease, and anemia can also develop. Dehydration is common in HPS patients, particularly for those with short bowel syndrome where bowel length and surface area are inadequate for sufficient absorption of fluid and nutrients, which can lead to high stool output.[1] The kidneys suffer the most as a result of repeated episodes of dehydration. A severe decrease in the perfusion of the kidneys as a result of increased gastrointestinal (GI) losses or poor oral intake can lead to acute kidney injury, which must be addressed immediately to prevent permanent damage. Lauverjat et al looked at the renal function of patients receiving long-term PN who had intestinal failure.

From [1]Home Nutrition Support, Cleveland Clinic, Cleveland, Ohio, USA; [2]FMC Liberty Dialysis, Colorado Springs, Colorado, USA; [3]Nutrition Support Consultant, Chesterland, Missouri, USA; [4]Cleveland Clinic, Cleveland, Ohio, USA; [5]Digestive Disease Institute, Cleveland Clinic, Cleveland, Ohio, USA; and [6]Intestinal Transplant Program, Cleveland Clinic, Cleveland, Ohio, USA.

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Corresponding Author:
Denise Konrad, RD, LD, CNSC, Nutrition Support Clinician, Cleveland Clinic, 9500 Euclid Ave TT2, Cleveland, OH 44195, USA.
Email: konradd2@ccf.org

Nearly 53% of patients had a decrease in renal function, and 71% of these cases were a result of dehydration.[2]

The complex process of monitoring HPS patients involves more than simply ordering and reviewing laboratory values. Clinicians need to evaluate the multiple medical aspects, including objective data (eg, weight, intake and output [I/O] data, vital signs, laboratory results) and physical symptoms (eg, excessive thirst, light-headedness, cramping in extremities, poor skin turgor, dark colored urine). When this comprehensive approach is taken, there are greater opportunities to identify and prevent readmissions related to dehydration.

Despite the possible difficulties, earlier literature demonstrated that HPS therapy represents a significant fiscal benefit when compared with the cost of hospital- or facility-based PN, but current economic data are limited.[3,4] An article by Landers highlighted how imperative it was for health care organizations to adopt a home-based care model due to demographic, clinical, economic, and technological forces.[4] This is supported by several earlier studies evaluating the economic benefits of HPN versus institutional-based PN.

In 2012, the Affordable Care Act mandated the Centers for Medicare and Medicaid Services to reduce payments to hospitals for readmissions that occur within 30 days of a previous discharge. The centers issue penalties that are determined by comparing hospital performance to the national average, then adjusting for other factors, such as patient demographics, income, education, housing, comorbidities, and patient frailty. These factors can affect outcomes more than medical treatment.[5] The rationale is that frequent readmissions suggest a lack of proper planning, communication, and continuity of care from the hospital and therefore should be penalized. Thirty-day readmission rates are 19%–20% for all Medicare patients, and the estimated associated costs of the preventable readmissions is >$17 billion annually.[6] Due to reduced reimbursement rates, it has become increasingly important for hospitals to find ways to reduce their readmission rates.

In 2010, our HPS service developed a protocol to educate HPS patients on the identification of the signs and symptoms of dehydration.[1] Another aspect of the protocol was to provide additional IVF to have on hand for immediate use for those patients at risk of developing dehydration (conditions that had potential for high-volume GI losses) or those who live long distances from the homecare pharmacy (Appendix 1). Our goal was to evaluate the effectiveness of our protocol by comparing 2009 and 2010 data and to assess healthcare costs avoided by treating dehydration at home versus emergency department (ED) visits and hospital readmissions.

Methods

A retrospective analysis was completed through an Institutional Review Board–approved clinical management database to identify all HPS patients during 2009 and 2010. Data collected included demographics (age and sex), primary diagnoses, HPS indication, presence of a fistula or enterostomy, type of diet, objective signs of dehydration (laboratory values [sodium, chloride, serum urea nitrogen, and creatinine], vital signs [heart rate and blood pressure if available], decreased body weight of ≥2 kg in 24 hours, urine output <1 L in 24 hours, increased enterostomy or GI losses, negative I/O data), physical signs of dehydration (dry mouth, excessive thirst, dark-colored urine, light-headedness, or cramping in extremities) patient or clinician identification of dehydration, dates of ER visits or hospital admission for dehydration if present, and compliance with infusion orders.

Table 1. Dehydration Parameters Used to Instruct Patients to Administer Intravenous Fluids.[a]

Type of Sign	Indicator
Objective	Change in laboratory values from baseline: sodium, chloride, serum urea nitrogen, creatinine
	Altered vital signs: heart rate and blood pressure (especially orthostatic hypotension)
	Decreased body weight ≥2 kg in 24 h
	Negative I/O data (O > I × 48 h)
	Urine output <1 L in 24 h
	Increased GI losses vs baseline
Subjective	Dry mouth
	Excessive thirst
	Dark colored urine
	Light-headedness
	Cramping in extremities

GI, gastrointestinal; I/O, intake and output.
[a]The home parenteral support clinician used these objective and subjective signs of dehydration to determine if patients needed additional intravenous fluids.

As part of the protocol implemented in 2010, all HPS patients received education on the signs and symptoms of dehydration from a nutrition support nurse and HPS clinician prior to hospital discharge. The nutrition support nurse completes lessons with the patient and/or caregiver, typically in 2 sessions (1 focused on catheter care and the other on home self-monitoring) that last anywhere from 2–4 hours or longer according to patients' needs. On the day of hospital discharge, the HPS clinician reviews key points of the lessons and answers any questions that the patient and/or caregiver may have. Patients were instructed to call the HPS service if they experienced any physical or objective signs of dehydration (Table 1). The homecare RN continued education in the home setting. Patients had laboratory values routinely ordered and drawn posthospital discharge to monitor for dehydration as well as electrolyte abnormalities and signs of catheter infection. Laboratory values were drawn more frequently when patients were initially discharged from the hospital with HPS or if an established patient had abnormal results. Laboratory tests were ordered weekly and then monthly as patients' laboratory results and HPS prescriptions gradually became stabilized. The HPS clinician initiated contact with the patient if dehydration was indicated from laboratory values or weekly I/O records, which are sent to the HPS service by the patient/homecare RN and evaluated for additional symptoms to recommend the

appropriate treatment. The HPS service instructed patients to call and report any problems with their HPS infusions or any unusual symptoms in between scheduled laboratory testing. Patients are seen in the outpatient clinic as determined by the managing HPS physician (within a month of initial hospital discharge, then every 3–6 months until they are stable enough for annual visits). Those patients with any frequent complications are followed more often in the office to allow for ongoing education, reinforcement of the care plan, and monitoring.

Dehydration was defined as negative fluid balance (output greater than input in the absence of medical intervention to cause diuresis), as documented on I/O records with at least 1 physical symptom and/or an alteration in laboratory markers of dehydration compared with baseline values. With the implementation of our protocol, the standard treatment for dehydration was 1 L of home IVF (HIVF) daily for 3 days in addition to the patient's regularly prescribed HPS infusions. Patients defined as high risk for dehydration or those living in far distances or rural areas received a standing order to have three 1000-mL electrolyte-free IVF bags on hand for use as directed by a HPS clinician. Patients were instructed to infuse IVF over an individualized time frame (typically 4 hours) as determined by the HPS clinician according to the type of tubing or pump available in the home setting, age, and other comorbid conditions. Dehydration was considered resolved as determined by reference laboratory values at completion of HIVF infusions and/or resolution of physical symptoms.[1]

Data are presented as means, standard deviations, and percentiles. Univariable analysis was performed to compare patients with dehydration episodes in 2009 and 2010. Student's *t* test or the nonparametric Wilcoxon rank sum tests were used for continuous variables, and Pearson's χ^2 test was used for categorical factors. To account for correlations among multiple episodes occurring in the same patient, generalized estimating equation for binary outcomes (logit link) was used to compare different outcomes and characteristics between the 2 study years. A *P* value <.05 was considered statistically significant. All analyses were performed with SAS 9.2 (SAS institute, Cary, NC).

For the cost avoidance analysis, data were collected regarding billing and coding for ED visits and hospital readmissions to evaluate their cost as compared with the cost of home treatment. For ED and hospital readmission data, our institute's finance department was consulted, and costs were based on the *International Classification of Diseases, Ninth Revision* code for dehydration (276.51). Direct and indirect costs were accounted for when calculating cost of treatment for each treatment setting. For ED visits and hospital admissions, costs and services directly related to patient care were included, as were indirect costs such as utilities and general overhead. Only admissions with dehydration as the primary diagnosis were included in the cost analysis. Hospital admissions for other, potentially more serious reasons with secondary diagnoses of dehydration were excluded, as these admissions would not have been avoided by treating dehydration in the home setting. Our institution's homecare pharmacy was contacted to determine associated costs of treating dehydration in the home setting, which included the cost of IVF bags, gravity pump, tubing, and nursing visit to instruct how to administer IVF.

Table 2. Hospital Admissions Among All Home Parenteral Support Patients: 2009–2010.[a]

Hospital Admissions	2009 (n = 294)	2010 (n = 308)
Total	404	469
Related to primary diagnosis	192 (47.5)	231 (49)
Related to HPS	123 (30.5)	136 (29)
Related to dehydration	13 (3.2)[b]	22 (4.8)[c]
Related to other reasons	89 (22)	102 (22)

[a]Values are presented as n (%).
[b]Episodes of dehydration identified, n = 83 (among 77 patients).
[c]Episodes of dehydration identified, n = 201 (among 102 patients).

Results

In 2009, 294 HPS patients (273 HPN and 21 HIVF) were active with our HPS service, which then increased to 308 patients (283 HPN and 25 HIVF) in 2010 (Table 2). In 2009, there were a total of 404 hospitalizations among all active patients: 192 (47.5%) readmissions were primary diagnosis related, 123 (30.5%) HPS related, and 89 (22%) for other reasons. Only 13 admissions (3.2% of readmissions) were dehydration related. Of the 294 HPS patients active in 2009, there were 83 episodes of dehydration identified in 77 patients (71 HPN and 6 HIVF). Overall hospital readmissions increased in 2010 to 469: 231 (49%) were primary diagnosis related, 136 (29%) HPS related, and 102 (22%) for other reasons. Twenty-two admissions (4.8% of readmissions) were due to dehydration. In addition, the number of dehydration episodes more than doubled to 201 among 102 patients (91 HPN and 11 HIVF). Furthermore, there were significantly more dehydration episodes per 100 patients in 2010 (28.2 in 2009 vs 60.9 in 2010; $P < .001$).

Of the 83 episodes of dehydration identified in 2009, 64 episodes (77.1%) were successfully treated at home, as compared with 6 ED visits (7.2%) and 13 hospital readmissions (15.7%). Eleven patients accounted for the 13 hospital readmissions, with 9 patients having 1 readmission and 2 patients having 2 readmissions each. After implementation of the protocol in 2010, we successfully treated 170 episodes (84.5%) in the home, with only 9 episodes (4.5%) requiring ED visits and 22 (11%) requiring hospital readmissions (Figure 1). Sixteen patients were responsible for the 22 readmissions in 2010: 13 patients had 1 readmission, and 3 patients had 2–4 readmissions each.

After dehydration was identified, it was determined whether the patient needed an increase in HPS volume or HPS infusion days or if no change was indicated owing to an acute episode of increased GI losses. In 2009 and 2010, there was no change to HPS volume almost half the time (45.8%). HPS volume was similarly increased in both years: 38.5% in 2009 versus 39.8% in 2010. An increase in HPS infusion days was seen in only

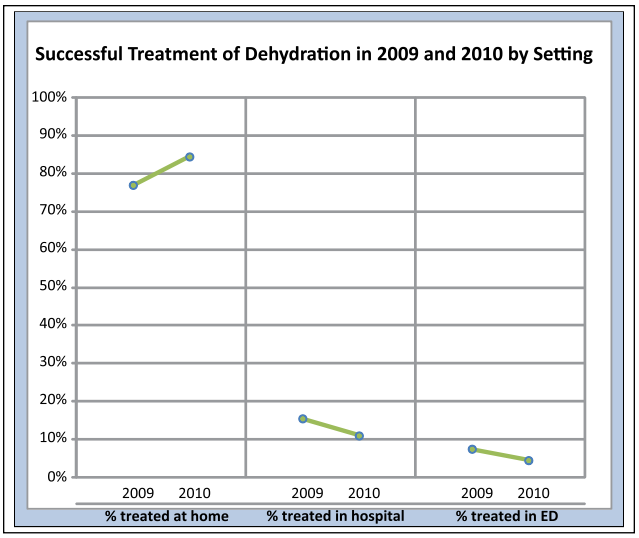


Figure 1. Treatment of dehydration improved from 2009 to 2010 and therefore reduced hospital admissions and emergency department (ED) treatment.

14.4% of episodes in 2009 and 2.5% of episodes in 2010. Significantly more patients had their as-needed IVF kept the same in 2010 versus 2009, indicating that more patients were ordered as-needed IVF for the first time in 2009 after they experienced dehydration (3.6% in 2009 vs 13.9% in 2010; P = .023). In a small number of patients (2 in 2009 vs 1 in 2010), PN volume was decreased, but the infusion days increased to prevent increased edema.

The average age of patients was 53 years, and 38% were male. The most common diagnoses of patients receiving HPS who had at least 1 episode of dehydration identified during the study period were Crohn's disease and cancer with malabsorption, fistula, or obstruction. Other indications included enterocutaneous fistula, intestinal obstruction, bowel ischemia, and GI dysmotility (Table 3). There were no significant differences between study years for underlying GI diagnosis, presence of enterostomy or fistula, or type of diet. The majority of patients were discharged on a regular or GI soft diet, and 75% of patients had a fistula, stoma, or both.

The most common symptoms of dehydration reported by all patients throughout the study period were decreased weight (45.4%), decreased urine output (42.3%), and increased GI losses (34.5%). The signs and symptoms of dehydration reported between the study years varied. In 2009, decreased weight (P = .002), nonspecific symptoms (P < .001), and no physical symptoms (P = .033) were more commonly reported. In 2010, dark-colored urine (P < .001) was more often reported, as identified in 30.7% of patients. In 2010, 60.4% of patients had I/O data that were consistent with negative fluid balance, as opposed to 40.3% of patients in 2009 (P < .001). Vital signs were affected in only a small percentage of patients throughout

Table 3. Home Parenteral Support (HPS) Indication Among Study Patients Who Experienced Dehydration: 2009–2010.[a]

Rationale	2009 (n = 77)	2010 (n = 102)
Malabsorption	27 (35.1)	51 (50)
Obstruction	22 (28.6)	25 (24.5)
Fistula	17 (22)	23 (22.5)
Ischemia	6 (7.8)	0 (0.0)
GI dysmotility	5 (6.5)	1 (1)
Chylothorax (NPO)	0 (0.0)	1 (1)
Failed enteral nutrition	0 (0.0)	1 (1)

GI, gastrointestinal; NPO, nothing by mouth.
[a]Values are presented as n (%). The majority of patients had malabsorption, intestinal obstruction, or fistula as the HPS indication throughout the study period.

the study period, which was not significantly different between years (9% in 2009 vs 11.9% in 2010; P > .55). Laboratory values were not always affected when the early signs of dehydration were recognized by patients. In 2009, laboratory values remained within normal limits in almost one-third of episodes, compared with only 18% in 2010. When laboratory values were affected, posttreatment values returned to normal in 42.3% of episodes in 2009. Successful correction of laboratory values increased to 56% in 2010.

HPS clinician-initiated contact to patients was significantly higher in 2010 (22% in 2009 vs 47% in 2010; P = .016). There was no significant difference in the occurrence of patients contacting the HPS service to report signs of dehydration between study years (43% in 2009 vs 33% in 2010; P = .74). The remaining episodes of dehydration were identified when a patient was seen in the outpatient clinic or by another healthcare professional contacting our service on behalf of the patient, with the exception of documentation that did not identify who initiated contact during the retrospective review.

The number of dehydration episodes per patient was significantly higher in 2010 (1–2 vs 1–8 episodes; P < .001). In 2009, 94% of patients had only 1 documented episode of dehydration, and 6% had 2 episodes. In contrast, 52% of patients in 2010 had 1 episode of dehydration; 26.5% had 2 episodes; and 21.5% had ≥3 episodes. On multivariable logistic regression, after adjusting for age and reason for therapy, patients were 16 times more likely to have multiple episodes of dehydration identified in 2010 (odds ratio = 16.4, 95% confidence interval = 5.2–51.9, P < .001). Patients who experienced excess thirst during at least 1 episode were 3.8 times more likely to have multiple episodes of dehydration than those that never reported thirst as a symptom (P = .012). Similarly, patients who were identified as being hypotensive were 33 times more likely to have >1 episode of dehydration than those who maintained normal blood pressure readings (P < .001). In addition, for every 5-year

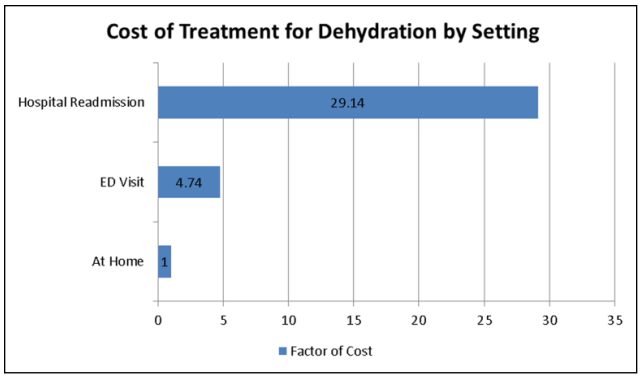


Figure 2. An emergency department (ED) visit costs almost 5 times as much as home treatment, and readmission costs 29 times more than home treatment.

increase in age, the likelihood of having >1 episode of dehydration increased by 20% (P = .015). The average days between episodes for patients with multiple episodes was significantly shorter in 2009 (11.5 vs 28.7 days; P = .041). In addition, patient compliance with the treatment plan was significantly higher in 2010 (92% vs 58%; P < .001).

Direct and indirect costs for resource areas vary between ED visits and admissions. For example, nursing costs equal 38% of total costs for a hospital admission, compared with only 12% for ED visits. Emergency room, intravenous therapy, and laboratory tests account for higher percentages of ED treatment as compared with admission costs. An ED visit costs almost 5 times as much as home treatment, and a readmission costs 29 times more than home treatment. Hospital admissions ranged from 1–6 days, with the average length of stay being 4 days (Figure 2).

Discussion

Our service has routinely treated the early signs of dehydration at home by utilizing additional IVF, even prior to the implementation of the protocol. However, delays in treatment occurred when patients did not have extra IVF on hand and had to wait for a delivery from the homecare pharmacy. Our present study set out to determine the effectiveness of our protocol, and it found that there were more than twice as many episodes of dehydration identified and treated at home in 2010 than in 2009. The increased number of dehydration-related episodes can be attributed to more patients having malabsorption as the indication for therapy in 2010 (35.1% in 2009 vs 50% in 2010; P = .003; Table 3). During this time, the intestinal rehabilitation and transplantation program was growing at our institution and therefore referred more patients to our service for HPS management. Additionally, clinicians and patients alike had an increased focus on monitoring for dehydration. Although there were more episodes of dehydration in 2010, a higher percentage were treated at home when compared with 2009 (84.5% vs 77.1%), and as a result, fewer episodes resulted in hospital care (15.5% in 2010 vs 22.9% in 2009).

Based on Medicare reimbursement rates, an admission for dehydration has a projected length of stay of 2.8 days. In the current study, the average length of stay was 4 days. We suspect that the longer length of stay for our patient population is due to the complexity of their underlying diseases and dependency on HPS. With the successful home treatment of dehydration, we potentially avoided 256 hospital days in 2009 and 680 hospital days in 2010. The average patient age was of working age, which means fewer missed days of work, leading to less economic hardship (due to missed wages) and likely improved quality of life.

Messaris et al found that readmission for patients with a diverting loop ileostomy was 16.9%, with the major cause being dehydration.[7] In 2011, researchers at Beth Israel Deaconess Medical Center looked to create a pathway to reduce readmission and facilitate education for patients with a new ileostomy.8 The readmission rate for dehydration was 15.5% prior to the implementation of the pathway but dropped to 0% in the study group that took part in the education program. This study also demonstrated that the postdischarge tracking of a patient's fluid intake and output was very effective in decreasing hospital readmissions.

More patients (44.1%) in 2009 in our study group simply reported feeling dehydrated and did not report specific symptoms that they felt. An increase in symptom-specific reporting seen in 2010 may be related to the education lessons provided by the nutrition support RN and to the discharge education provided by the HPS clinician. At hospital discharge in 2010, the HPS clinician would (1) make patients aware that they would be receiving additional IVF with their first delivery, (2) explain the purpose of these fluids, and (3) review when to call our service for signs of dehydration. Interestingly, more patients in 2010 reported negative fluid balance based on their daily I/O records (60.4% vs 40.3%), which may also be related to the focused discharge education provided in 2010. Aside from increased patient education, the difference in reported symptoms and contact initiation may be due in part to the documentation style of each clinician. If the clinician documented only some of the patient-reported symptoms instead of all of them, there would be no way to retrospectively capture the missing data. The documentation of blood pressure and heart rate is limited, since vital signs were evaluated only during homecare nursing visits or if a patient had access to a blood pressure cuff at home. Homecare RNs routinely see patients once a week or less often, if bloodwork is not ordered and a patient or caregiver is independent with catheter care.

Patients may have identified the early physical signs of dehydration before an impact was seen on laboratory studies, therefore explaining how laboratory results were not affected or resolved in some episodes. We suggest that the

episodes that did not show resolution in laboratory values could be due to one or more of the following reasons: (1) laboratory testing was done too early before full correction of the fluid balance occurred; (2) patients had bloodwork drawn too late to assess for correction of dehydration; (3) ongoing fluid losses required a greater volume correction than what was ordered; and (4) patients were not infusing extra fluids as ordered.

In addition to the inherent flaws based on the retrospective study design, other limitations exist. There were several costs not accounted for in this study, including costs associated with additional laboratory monitoring, transportation to and from outpatient laboratories for those without homecare nursing, and delivery charges associated with sending HIVF to the patients. In addition, extra nursing visits for laboratory draws were not included for those patients who did not go to an outpatient laboratory, as these costs vary among nursing agencies and insurance companies. Due to the nature of our retrospective design, it was not possible to track individual patients and costs accrued during their hospital course, as done in earlier studies. In addition, costs were based solely on our institution's charges, as we were unable to account for a difference in cost when patients were treated at other hospitals or they utilized another homecare pharmacy.

While there were likely multiple patients receiving service in both 2009 and 2010, it is primarily the new patients who are affected by the formal protocol initiated in 2010. As we noted in our previous study, HPS patients (>1-year therapy) can easily identify the common signs and symptoms of dehydration and over time may not necessarily contact our service prior to administering additional IVF (this is discouraged, but we have been aware of the occurrence after the fact in some outlying cases). However, these patients still had documented episodes of dehydration, and the patient with the most episodes was receiving HPS for 10 years. This demonstrates the ongoing need for patient education no matter how long a patient has been receiving a specific therapy. Furthermore, there is no way to retrospectively identify dehydration episodes if the HPS clinician fails to document the assessment of dehydration or the order to use the HIVF. In addition, there may have been instances when a patient was admitted to another hospital for dehydration and our service was not informed. Consequently, we may not have captured all episodes of dehydration experienced by patients during the study period.

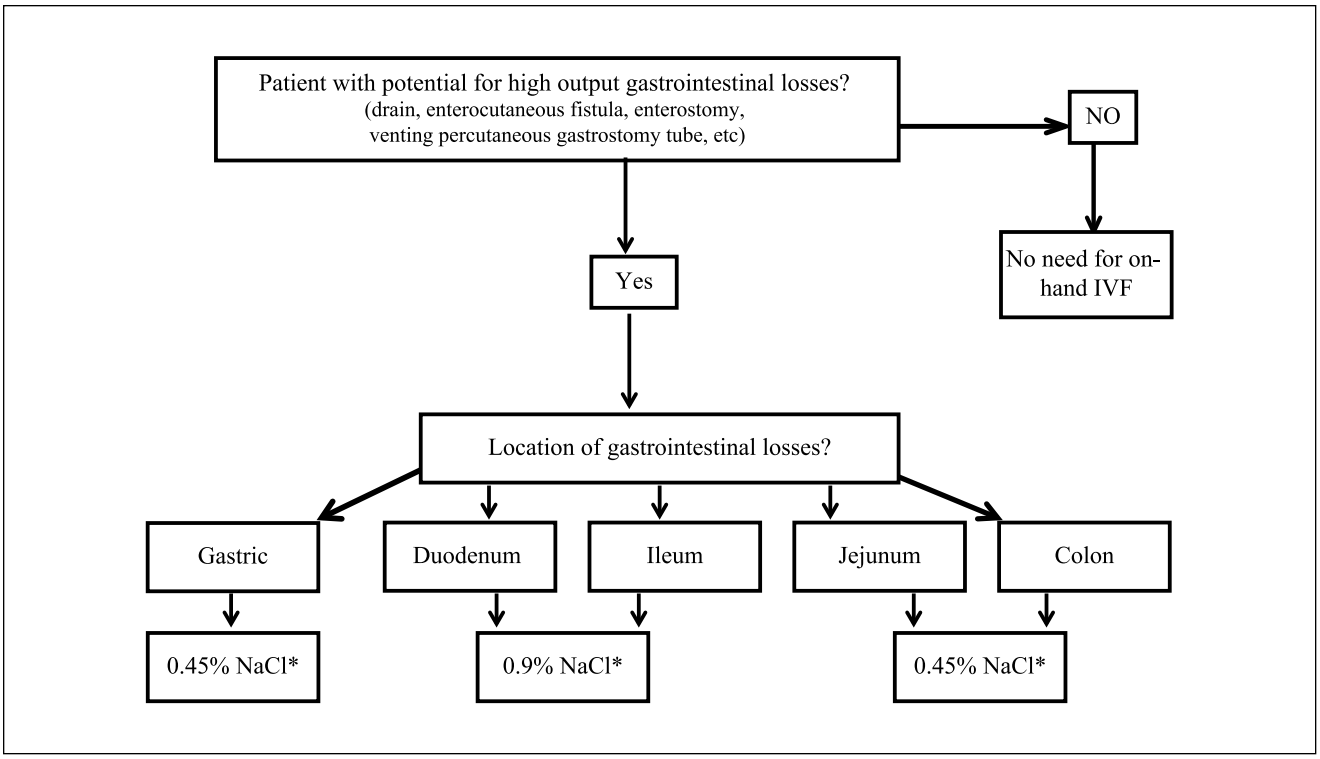
Future research should focus on further identifying characteristics associated with the increased risk of dehydration, such as those factors accounted for by the Centers for Medicare and Medicaid Services when examining hospital readmissions (eg, income, education, housing). Additionally, quality-of-life measures should be evaluated to better understand the comprehensive benefits of treating dehydration at home and not only those associated with reducing healthcare costs.

Conclusion

It is becoming more important for hospitals to find ways to reduce hospital readmissions because of the Affordable Care Act. HPS complications leading to readmissions can manifest as a result of poor discharge education or planning, a lack of patients' compliance with treatment, or both. Patients with the inability to perform self-care or those who have poor home support may need to consider residing at a long-term acute care or skilled nursing facility for the duration of therapy or until deemed appropriate for homecare. Proper education and discharge assessments are paramount to determining if HPS is appropriate. Our HPS service has always required patients or caregivers to receive education on central line care, potential HPS complications, and how to keep strict I/O records, as part of our program to help ensure proper management of their HPS. Selecting patients for HPS therapy who will follow physician recommendations and be proactive in recognizing potential complications is crucial for successful outcomes. As with many home therapies, a failure to determine the optimal treatment modality for a patient can lead to a loss of quality of life and blunt any economic gain. Reducing preventable hospital admissions and ED visits is paramount to patients who are chronically ill and receiving long-term parenteral support. Treating these patients in the home setting is valued not only by the hospital system but also by patients who are burdened by frequent hospital admissions due to other health conditions.

The current study's cost analysis shows the value of HPS clinicians in identifying and treating dehydration at home. It also demonstrates the benefits of having a multidisciplinary team manage HPS patients. The HPS clinicians (dietitians, nurses, and pharmacists) work in close contact with HPS physicians in clinical decision making related to patient care. HPS clinicians and physicians develop protocols to expedite care plan treatment for a large outpatient service. Patients have 24-hour access to the HPS clinicians to triage critical cases to physicians. Multiple HPS clinicians make caring for a large HPS population possible.

In our study, there were more than twice as many episodes of dehydration identified and treated at home in 2010 versus 2009. The most common symptoms of dehydration reported were decreased weight, decreased urine output, and increased GI losses. Excessive thirst, hypotension, and older age were factors found to be associated with multiple occurrences of dehydration. By selecting appropriate HPS patients, providing resources to have on hand, and having clinicians monitoring dehydration at a heightened level, we were able to resolve dehydration at home in 84.5% of episodes. Furthermore, by reducing ED visits and hospital readmissions, healthcare costs were avoided by a factor of 29 when home treatment was successful. This likely had a positive effect on patients' quality of life.



Appendix 1. Algorithm for identifying patients at risk for dehydration. IVF, intravenous fluids; 0.45% NaCl, 1/2 normal saline; 0.9% NaCl, normal saline. *Type of fluid prescribed may vary per clinical judgment or presence of comorbidities. Figure reprinted with permission from Konrad D, Corrigan ML, Hamilton C, Steiger E, Kirby D. Identification and early treatment of dehydration in home parenteral nutrition and home intravenous fluid patients prevents hospital admissions. *Nutr Clin Pract.* 2012;27:802-807.

Statement of Authorship

D. Konrad, S. Roberts, and M. L. Corrigan contributed to the conception/design of the research and the acquisition, analysis, or interpretation of the data; D. Konrad and S. Roberts drafted the manuscript; and C. Hamilton, E. Steiger, and D. F. Kirby interpreted the data. All authors critically revised the manuscript, read and approved the final manuscript, and agree to be fully accountable for ensuring the integrity and accuracy of the work.

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Novel, Family-Centered Intervention to Improve Nutrition in Patients Recovering From Critical Illness: A Feasibility Study

Andrea P. Marshall, RN, PhD[1]; Margot Lemieux, RD[2]; Rupinder Dhaliwal, RD[2,3]; Hilda Seyler, RD[4]; Kristen N. MacEachern, RD, MSc[5]; and Daren K. Heyland, MD[6]

Abstract

Background: Critically ill patients are at increased risk of developing malnutrition-related complications because of physiological changes, suboptimal delivery, and reduced intake. Strategies to improve nutrition during critical illness recovery are required to prevent iatrogenic underfeeding and risk of malnutrition. The purpose of this study was to assess the feasibility and acceptability of a novel family-centered intervention to improve nutrition in critically ill patients. *Materials and Methods:* A 3-phase, prospective cohort feasibility study was conducted in 4 intensive care units (ICUs) across 2 countries. Intervention feasibility was determined by patient eligibility, recruitment, and retention rates. The acceptability of the intervention was assessed by participant perspectives collected through surveys. Participants included family members of the critically ill patients and ICU and ward healthcare professionals (HCPs). *Results:* A total of 75 patients and family members, as well as 56 HCPs, were enrolled. The consent rate was 66.4%, and 63 of 75 (84%) of family participants completed the study. Most family members (53/55; 98.1%) would recommend the nutrition education program to others and reported improved ability to ask questions about nutrition (16/20; 80.0%). Family members viewed nutrition care more positively in the ICU. HCPs agreed that families should partner with HCPs to achieve optimal nutrition in the ICU and the wards. Health literacy was identified as a potential barrier to family participation. *Conclusion:* The intervention was feasible and acceptable to families of critically ill patients and HCPs. Further research to evaluate intervention impact on nutrition intake and patient-centered outcomes is required. (*Nutr Clin Pract*. 2017;32:392-399)

Keywords

nutrition; critical illness; family centered care; malnutrition; intensive care unit; patient care team; family

Background

Critically ill patients are at increased risk of developing malnutrition-related complications because of physiological changes and reduced intake.[1] As many as 40% of patients may experience malnutrition during their hospital stay, some as a result of iatrogenic underfeeding.[2] The reasons for poor nutrition are numerous and are linked to the reduced delivery and nutrition intake by the patient. The significant consequences of underfeeding in critical illness require early intervention with nutrition therapy. To date, large-scale, multifaceted interventions have failed to overcome barriers to nutrition delivery in the critically ill and to demonstrate meaningful improvements in nutrition practices.[3,4]

Strategies for optimizing nutrition intake for critically ill patients must be considered throughout the recovery trajectory. As patients transition to an oral diet, intake may be poor while nutrition needs of the patient remain high.[5,6] Environmental factors, such as fasting for tests or procedures, may inhibit oral intake, and together with reduced food choice and inability to independently manage oral intake, suboptimal nutrition intake may occur. Other factors, including weakness, therapeutic diet prescription, and lack of appreciation of nutrition and physical barriers, may further contribute to reduced nutrition. It is also possible that poor nutrition delivery also occurs because patients and families view nutrition as only moderately important in the scope of their recovery. A number of interventions have been developed to improve this for hospitalized patients, including protected mealtimes, feeding assistance, and use of oral nutrition supplements.[7–9] Despite many studies on the use of oral nutrition supplements and other interventions, underfeeding still exists; hence, alternative methods to improve nutrition intake are required.

Because the problem of malnutrition and underfeeding spans the entire journey of critical illness from intensive care unit (ICU) admission to hospital discharge, a nutrition intervention that addresses the recovery trajectory is warranted. As patients recover and move through the hospital system, the continuity of care can be compromised, which may result in an inconsistent approach to care that is not responsive to the patient's changing needs during an illness.[10] We propose a novel, family-centered intervention that educates family members of critically ill patients about the importance of nutrition

in recovery and encourages them to act as advocates for the delivery of prescribed nutrition intake. Through advocating for best nutrition practice, we anticipate that families will participate in a patient-level audit and feedback and partner with healthcare providers to ensure optimal nutrition delivery. We believe that by empowering families with knowledge about nutrition and how to engage healthcare professionals (HCPs) about nutrition, this will increase the value HCPs place on nutrition and change their behavior. This family-centered approach aligns with an international movement toward recognizing the interdependency between the patient (and family) and the professional to achieve optimal health outcomes[11] and is consistent with other approaches to family-centered care in the ICU.[12–15] Engaging family members as partners within the multidisciplinary team may be a promising strategy with potential to improve patient outcomes, but a feasibility and acceptability assessment is needed prior to testing the effectiveness of such an intervention. The purpose of this study was to assess the feasibility of a novel family-centered intervention designed to improve nutrition across the continuum of care of critically ill patients.

Materials and Methods

Study Design

Guided by the Medical Research Council's Developing and Evaluating Complex interventions,[16] we undertook a prospective cohort study to test the hypothesis that an intervention designed to educate family members of critically ill patients about the importance of nutrition in recovery from critical illness and encourage them to act as advocates for best nutrition practices was both feasible and acceptable. A 3-phase, sequential pilot study was conducted to progressively refine and evaluate the intervention in multiple contexts. Qualitative data from phases 1 and 2 are published elsewhere.[17] This feasibility assessment lacks a control group, and therefore the efficacy of the intervention cannot be determined. Intervention efficacy is the focus of the IMPACT trial (NCT02920086).

Setting

The study was conducted in 2 Australian and 2 Canadian adult ICUs. Hospital bed numbers ranged from 320–520; ICU bed numbers ranged from 14–20. All ICUs provided 1:1 nursing care for ventilated patients and had an enteral nutrition (EN) protocol in place. Each ICU had dietitian support available, although this was variable, and the full-time equivalent ranged from 0.4–1.0. Dietitian follow-up after discharge from ICU was available at all sites.

Sample

We recruited family members of ICU patients who were expected to remain in the ICU for at least 48– 72 hours. Interim evaluation after completion of the first phase resulted in modifications to inclusion criteria and the intervention. Details of inclusion and exclusion criteria are provided in Supplementary Table S1. HCPs and their families were also enrolled in the study.

Intervention

Comprehensive intervention description of the interventions is reported elsewhere, including the theoretical underpinnings on which the intervention was based.[17] In keeping with a patient- and family-centered approach,[18–20] the intervention was iteratively developed across the 3 phases of the pilot study. Phase 1 included a brief patient nutrition history from the family member and a focused nutrition education session supplemented with a printed resource. In phase 2, a nutrition diary was included as an additional component. The diary was to be completed by the family at each visit, once the patient had resumed oral intake by documenting the amount of food and supplements consumed by

From the [1]National Health and Medical Research Council Centre for Research Excellence in Nursing Interventions for Hospitalised Patients, School of Nursing and Midwifery, Menzies Health Institute, Griffith University and Gold Coast Health, Southport, Queensland, Australia; [2]Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada; [3]Metabolic Syndrome Canada, Kingston, Ontario, Canada; [4]Clinical Nutrition and Food Services, Halton Healthcare, Oakville Trafalgar Memorial Hospital, Oakville, Ontario, Canada; [5]Clinical Nutrition and Critical Care, Mount Sinai Hospital, Toronto, Ontario, Canada; and the [6]Department of Critical Care Medicine, Queen's University and Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, Ontario, Canada.

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Corresponding Author:
Andrea P. Marshall, RN, PhD, National Health and Medical Research Council Centre for Research Excellence in Nursing Interventions for Hospitalised Patients, School of Nursing and Midwifery, Menzies Health Institute, Griffith University and Gold Coast Health, Room E2.015, Parklands Drive, Southport, QLD 4214, Australia.
Email: a.marshall@griffith.edu.au

the patient at each meal. Details of the intervention used in phase 3 are provided in Supplementary Table S2.

Based on our learning from phases 1 and 2, we modified the intervention delivery time from 48–72 hours and extended the time during which the intervention could be delivered within the first week after ICU admission to accommodate individual family circumstances. Additional intervention components included enhanced dietitian follow-up in the ICU, reinforcement of the nutrition education provided to families prior to ICU discharge, handover from the ICU to the ward dietitian, and documentation of nutrition intake. Outcome questions were modified to allow evaluation of changes to the intervention.

Data Collection

Data collection was complete in July 2015. In phases 1 and 2, data were collected for 49 patients over a 15-month period; in phase 3, data were collected for 26 patients over a 9-month period. Organizational characteristics of the hospital and ICU were collected, including geographic location, hospital size, number of ICU beds, dietitian coverage in the ICU, the implementation of any nutrition protocol and/or algorithm used, and availability of post-ICU discharge dietitian follow-up.

Data to inform feasibility assessment, including the patient eligibility, recruitment, and retention rates, were also collected. The study investigators kept detailed notes regarding study implementation and challenges or modifications to the study protocol. Intervention delivery time was collected in the third phase of the pilot study.

Patient-specific data included demographics and nutrition intake in the ICU. While the patient was in the ICU, we collected data regarding prescription and delivery of EN in the ICU, time to EN initiation, route of feeding, interruptions to EN, and calories and protein prescribed/received for each day from ICU admission until discharge. We did not collect protein or calorie intake from oral diet or supplements. An estimate of nutrition risk was obtained from the families by asking about recent weight loss and reduced food intake in the past week.[21]

Demographic data were collected from families and HCPs who also provided their perspectives of the intervention acceptability. Survey questions were developed and refined for each phase of intervention evaluation. In phases 1 and 2, a 7-question survey comprising binary and Likert scale questions was given to family members. Detailed qualitative evaluation of the nutrition intervention was collected during phases 1 and 2 of the study and is reported elsewhere.[17] These qualitative data informed a quantitative survey developed for phase 3. The phase 3 survey contained the 7 original questions used previously plus an additional 20 questions about the intervention, 6 that were open-ended responses. See Supplementary Table S3 for example of questions. The healthcare provider survey contained 19 questions about the intervention, 4 that were open-ended responses. The survey was tested with volunteers before use to evaluate comprehension and clinical sensibility.

Data Analysis

Descriptive statistics were used to report organization, patient-level clinical data, and survey responses. No corrections were made for missing data, and frequencies were reported for those cases where complete data were available. Mean and mode of Likert scale questions were reported, and content analysis was used for open-ended questions. We judged intervention acceptability as occurring when (1) >80% of families and HCPs viewed the introduction of the intervention in the healthcare setting as being acceptable and (2) where families would be willing to participate in the intervention again, if given the opportunity. Feasibility was determined through (1) ability to recruit participants eligible for the study and (2) to retain at least 80% of patients and families in the study until hospital discharge. The study was approved by the relevant local hospital ethics committee with consent received from all participants.

Results

In phases 1 and 2, 16.2% of patients admitted to the ICU were eligible for the study, and in phase 3, after refinement of the inclusion criteria, the eligibility increased to 42.8%. There were 171 eligible patients and families. We approached 113 and obtained consent from 75 patients and family members (consent rate 66.4%). Reasons consent was not obtained from family members included inability to contact the family (n = 22; 13%), the research coordinator not being available (n = 15; 9%), family dynamics (n = 9; 5%), and the doctor deeming the patient ineligible (n = 7; 4%). Fifty-six HCPs also contributed data to this study. We achieved 100% compliance with intervention delivery and completion of the nutrition history. Most nutrition diaries were returned (n = 23; 82.0%), and 72% (n = 20) of families completed the phase 3 survey. Overall, we retained 52 (69.3%) of family participants to the end of the study; 5 patients died in the hospital, and 18 were lost to follow-up.

Patient demographic and nutrition intake data are detailed in Table 1. More than half of the patients were male, with a mean age of 59 years, and had a medical diagnosis on admission (almost one-third were admitted with a respiratory diagnosis). Nutrition prescription of protein and calories was 1.2 g/kg and 22.7 kcal/kg, respectively. Total caloric adequacy, represented as the percentage of prescribed calories delivered, was approximately 61.4%; protein adequacy was 55.4%.

Demographic details of family participants are provided in Table 2. Most family participants were female, with more than half older than 65 years. A third of participants were employed full-time, and most visited daily. Data were not obtained from 20 family members because of loss to follow-up.

For the evaluation of the intervention acceptability through surveys, most family members indicated that they would participate again if given the opportunity to do so (51/53; 81.0%) and would recommend others to participate in this nutrition

Table 1. Patient Demographic and Nutrition Intake Data.

Variables	Descriptor	Value[a]
Age, y		59.3 ± 20.1 (18.0–94.0)
Male		43 (57.3)
Primary ICU diagnosis	Respiratory	24 (32.0)
	Gastrointestinal	18 (24.0)
	Neurologic	12 (16.0)
	Sepsis	6 (8.0)
	Cardiovascular	6 (8.0)
	Trauma	4 (5.3)
	Metabolic	1 (1.3)
	Renal	2 (2.7)
	Other	2 (2.7)
ICU admission type	Medical	44 (58.7)
	Surgical elective	8 (10.7)
	Surgical emergency	23 (30.7)
Charlston comorbidity index		1.3 ± 1.7 (0.0–8.0)
APACHE II score		22.1 ± 7.8 (3.0–40.0)
LOV, d		9.8 ± 11.0 (0.3, 61.3)
ICU LOS, d		12.6 ± 10.4 (0.9–61.5)
Hospital LOS		26.0 ± 16.9 (1.2–68.8)
ICU mortality		7 (9.3)
Hospital mortality		8 (10.7)
BMI, kg/m^2		28.2 ± 9.2 (15.4–90.4)
MST score ≥2		18 (24.0)
Prescribed calories	kcal/kg	22.7 ± 6.1 (10.0–46.2)
	kcal/d	1726.2 ± 299.5 (1073.6–2458.0)
Prescribed protein	g/kg	1.2 ± 0.3 (0.5–2.3)
	g/d	95.4 ± 18.1 (53.0–140.0)
Total caloric adequacy		61.4 ± 44.0 (0.0–251.7)
Total protein adequacy		55.4 ± 40.5 (0.0–195.7)
Initiation of EN (hours since admission)		28.8 ± 25.6 (1.1–207.3)
EN interruptions (% of patient days)		34.2 ± 47.5 (0.0–100.0)

APACHE II, Acute Physiologic and Chronic Health Evaluation II; BMI, body mass index; EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay; LOV, length of ventilation; MST, malnutrition screening tool.
[a]Data are presented as mean ± SD (range) or number (%).

Table 2. Family Participant Characteristics.[a]

Characteristic	Category	No. (%)
Sex	Male	24 (32.9)
	Female	39 (53.4)
Age, y	18–24	1 (4.8)
	25–34	9 (17.6)
	35–44	8 (21.3)
	45–54	11 (32.7)
	55–64	17 (47.3)
	65+	18 (57.7)
Relationship	Spouse	39 (53.4)
	Child	12 (16.4)
	Parent	10 (13.7)
	Grandparent	1 (1.4)
	Close friend	1 (1.4)
Employment	Full-time	16 (34.0)
	Part-time/casual	7 (14.9)
	Retired/not working	11 (23.4)
Highest education level	Elementary/some high school	18 (24.7)
	High school	12 (16.4)
	College diploma/some college	17 (23.3)
	University	12 (26.5)
Anticipated visiting	Daily	58 (79.5)
	Every other day	2 (2.7)
	3 times a week	1 (1.4)

[a]Not all participants provided data for all categories.

education program (52/53; 98.1%). In the ICU, 47 of 52 (90.4%) family members indicated they were satisfied or very satisfied with nutrition care compared with 29 of 47 (61.7%) in relation to nutrition care received on the ward. Family members also felt that involvement in the study made it easier to ask questions about nutrition specifically (n = 16/20; 80.0%) and to pose additional questions to the healthcare team about the patient's management in general (n = 18/20; 90.0%). As standalone strategies, the education session was considered more helpful than the printed resource, although both together were also viewed favorably. Most family participants (n = 18/21; 85.7%) were comfortable participating in the nutrition intervention, although for some (n = 7/21; 33.3%), their level of personal stress influenced the ability to understand information provided in the education session. Most participants (10/21; 47.6%) identified the period of time soon after the patient was stable as being the best time to deliver the education session. The printed resource was reviewed or reread by over one-third of participants, and the majority shared this information with other family members. The nutrition diary was used daily by most participants (n = 17/20; 85%) and also considered easy to use (n = 18/20; 90.0%), with most participants preferring the diary to be in paper format vs electronic/other format.

Most family members rated knowing whether the patient was meeting his or her nutrition goals as being important or very important in the ICU (18/20; 90.0%) and on the ward (17/19; 73.7%) This information was often provided by HCPs in the ICU without families needing to request the information (n = 14/20; 70.0%), but this occurred to a lesser extent on the wards (n = 9/18; 50.0%). Families asked questions of HCPs at least sometimes in both clinical contexts (n = 15/21; 71.4% vs n = 17/20; 85.0%), and most participants indicated that health professionals were receptive or very receptive to the questioning, although receptiveness to questions was considered better for the ICU than the ward (n = 17/20; 85.0% vs n = 14/19; 73.7%).

Of the 56 HCPs surveyed about the nutrition intervention, 37.6% (21/56) had been involved in the care of a patient in the study. Most HCPs were female (n = 45; 77.6%), and the mean (standard deviation [SD]) years of experience was 12 ± 8.2. Forty-eight (84.2%) were employed full-time, and most (n = 33;

56.9%) were registered nurses; 9 were doctors and 14 were allied health professionals. Twenty-eight (48.3%) HCPs had a bachelor's degree as their highest qualification, and 21 (36.3%) held a postgraduate qualification.

Survey responses are provided in Table 3. HCPs were in agreement that families should partner with them to achieve optimal nutrition in both the ICU and the ward areas, with nursing and allied health considered most likely to support family partnerships. Family advocacy and involvement in clinical decisions about nutrition were also supported in both contexts but more so when patients were on the ward. Some HCPs perceived a lack of knowledge on the part of family members, particularly in the context of critical illness, as limiting their ability to advocate for optimal nutrition. Families were not considered in a position to determine how much information should be provided to them; rather, dietitians were seen as best placed to determine how much and what information families received about the patient's nutrition status and nutrition plan.

Discussion

This novel approach to improving nutrition intake during and following recovery from critical illness is acceptable to families and health professionals and feasible to undertake. Participation in the nutrition intervention was well received, with most family members indicating they would participate again or recommend participation to others. The materials used to provide family members with information on nutrition were well received and easily understood. Importantly, involvement in the study made it easier for family members to ask health professionals nutrition-specific questions as well as questions more generally.

The intervention is consistent with the principles of patient- and family-centered care. The intervention encouraged families to interact with all health professionals in the area of nutrition care, further emphasizing the importance of multidisciplinary approaches to optimizing nutrition intake of patients throughout the period of critical illness recovery. However, different levels of acceptance of family partnerships were evident in our data, and this variability should be considered when developing and implementing family-centered interventions in critical care and strategies implemented to facilitate this approach. At the organizational level, a variety of strategies have been articulated to support patient and family partnerships such as developing governance structures and a leadership culture that values and supports patient and family engagement.[22] These approaches are essential at all levels of the organization and should be considered when developing and implementing family-centered interventions.

Nutrition care in the hospital requires a multidisciplinary approach to achieve optimal delivery and intake of protein and energy.[23] In keeping with this approach, we have developed and tested this multifaceted intervention with a multidisciplinary team and, as recommended,[22] also included families in

Table 3. Healthcare Providers.

Statement	ICU, No. (%)	Ward, No. (%)	*P* Value
I support the notion of families partnering with healthcare professionals to achieve optimal nutrition.			
Disagree/strongly disagree	1 (2.2)	0 (0)	.0005
Neutral	4 (8.9)	1 (2.2)	
Agree/strongly agree	40 (88.9)	44 (97.8)	
Most doctors I know would support the notion of families partnering with healthcare professionals to achieve optimal nutrition.			
Disagree/strongly disagree	3 (6.8)	0 (0)	1.00
Neutral	8 (18.2)	10 (22.7)	
Agree/strongly agree	33 (75.0)	34 (77.3)	
Most nurses I know would support the notion of families partnering with healthcare professionals to achieve optimal nutrition.			
Disagree/strongly disagree	1 (2.3)	0 (0)	.55
Neutral	4 (9.1)	3 (6.8)	
Agree/strongly agree	39 (88.7)	41 (93.2)	
Most allied health professionals I know would support the notion of families partnering with healthcare professionals to achieve optimal nutrition.			
Disagree/strongly disagree	1 (2.2)	1 (2.2)	.45
Neutral	6 (13.3)	4 (8.9)	
Agree/strongly agree	38 (84.4)	40 (88.9)	
Families are best able to determine how much information they need about the patient's nutrition status and nutrition plan.			
Disagree/strongly disagree	17 (37.7)	17 (37.7)	.63
Neutral	12 (26.7)	11 (24.4)	
Agree/strongly agree	16 (35.6)	17 (37.7)	
Nurses should determine how much information families receive about the patient's nutrition status and nutrition plan.			
Disagree/strongly disagree	19 (42.3)	20 (44.5)	1.00
Neutral	12 (26.7)	14 (31.1)	
Agree/strongly agree	19 (22.2)	11 (24.5)	
Dietitians should determine how much information families receive about the patient's nutrition status and nutrition plan.			
Disagree/strongly disagree	2 (4.4)	2 (4.4)	1.00
Neutral	7 (15.6)	7 (15.6)	
Agree/strongly agree	36 (80.0)	36 (80.0)	
Doctors should determine how much information families receive about the patient's nutrition status and nutrition plan.			
Disagree/strongly disagree	7 (15.5)	7 (15.5)	1.00
Neutral	15 (33.3)	15 (33.3)	
Agree/strongly agree	23 (51.2)	23 (51.2)	
Families should be encouraged to advocate for best nutrition practice.			
Disagree/strongly disagree	1 (2.2)	0 (0)	.18
Neutral	5 (11.1)	2 (4.4)	
Agree/strongly agree	39 (86.7)	43 (95.5)	
Families are not present enough to effectively participate in promoting optimal nutrition.			

(continued)

Table 3. (continued)

Statement	ICU, No. (%)	Ward, No. (%)	*P* Value
Disagree/strongly disagree	11 (25.0)	10 (22.7)	.07
Neutral	18 (40.9)	13 (29.5)	
Agree/strongly agree	15 (34.1)	21 (47.8)	
It takes too much time to include families in discussions about nutrition.			
Disagree/strongly disagree	30 (66.7)	32 (71.1)	.38
Neutral	7 (15.6)	5 (11.1)	
Agree/strongly agree	8 (17.7)	8 (17.7)	
I believe that families should be provided with the opportunity to discuss their concerns about nutrition with healthcare providers.			
Disagree/strongly disagree	0 (0)	0 (0)	1.00
Neutral	0 (0)	0 (0)	
Agree/strongly agree	45 (100.0)	45 (100.0)	
Families do not have enough knowledge to enable them to advocate for optimal nutrition practice.			
Disagree/strongly disagree	9 (20.0)	10 (22.3)	.38
Neutral	16 (35.6)	16 (35.6)	
Agree/strongly agree	20 (44.5)	19 (42.2)	
Families do not have enough knowledge to participate in conversations about optimal nutrition for critically ill patients.			
Disagree/strongly disagree	13 (30.2)	16 (37.2)	.02
Neutral	7 (16.3)	9 (20.9)	
Agree/strongly agree	21 (47.1)	18 (41.9)	
Healthcare providers should make decisions about a patient's nutrition management without input from the family.			
Disagree/strongly disagree	33 (75.0)	37 (84.1)	.06
Neutral	8 (18.2)	7 (15.9)	
Agree/strongly agree	3 (6.8)	0 (0)	

ICU, intensive care unit.

this process. The intervention was informed by the principles of patient-centered care, which incorporate involvement of family and friends in decision making and advocacy.[24] Improvement in health outcomes as a result of patient participation is well described,[25] but in the context of critical illness, patient participation is often limited; thus, families become integral to providing patient-centered care.[19,20] Our survey data indicate that 85.7% family members who participated felt comfortable or very comfortable with the intervention, with two-thirds indicating that their personal stress did not distract from their understating of the information provided. This indicates that families were welcoming of the opportunity to partner with health professionals in nutrition care. Likewise, HCPs were also supportive of this approach, but there was greater acceptance when these partnerships were considered in the context of the post–critical illness period (ie, on the ward). And although the sample is small, data suggest that HCPs consider nurses and allied health professionals to be more supportive of the notion of family partnerships than doctors.

Open communication between families and the healthcare team is essential to achieving patient- and family-centered care[26] and a requirement for shared decision making.[27] While many factors influence effective communication,[28] the intervention appeared to assist families to initiate communication, not only asking nutrition-related questions but also seeking other information from the healthcare team. When questions were asked of HCPs, most were receptive, which is of importance when interacting with families[29] and likely to foster future family-initiated communications.

Nevertheless, there may be challenges when implementing interventions such as ours, particularly when variability in HCPs' receptiveness to family partnerships, where shared decision making or collaboration in care may be limited. Although shared decision making is endorsed by critical care organizations, there remains a lack of clarity about how or when this should be enacted.[27] In our study, healthcare staff frequently communicated information to family members about the patient's nutrition in the ICU, but this was perceived to occur only about half the time while the patient was on the ward. Another factor influencing shared decision making is low health literacy, which may prevent participation in meaningful healthcare decisions for up to one-third of patients.[30] Less is known, however, about the health literacy of family members, particularly in the context of critical care.[31] Despite health professionals' concerns about health literacy, most family participants in our study indicated that the intervention provided them with information that they did not know but were able to comprehend and felt comfortable discussing with health professionals. With variable levels of health literacy and baseline knowledge, it is important to work with families to determine their individual needs, recognizing that addressing any knowledge gap is an essential first step to improve families' capability and capacity to advocate for optimal nutrition.

The acceptability of the intervention to families and health professionals suggests that the impact of this intervention on short-term and long-term patient outcomes should be evaluated. The lessons we have learned from evaluating the feasibility of this intervention can inform future work. In evaluating feasibility, we assessed intervention fidelity and enrollment and retention rates, setting a target of 80% for both. While we achieved our target for participant retention, our consent rate was short of our goal but similar to that reported in other studies[32] or reported in trials where consent was obtained from family members.[33] We acknowledge a potential for selection bias, which may have occurred because consenting families may have viewed the intervention positively from the outset. In our planning, we may have underestimated the extent to which factors prevented consent being obtained. These factors include availability of research staff to obtain consent and of family to give consent, with these 2 factors accounting for over one-fourth of missed opportunities. Obtaining consent from family members was more challenging for ICUs where patients were admitted from wider

geographical areas, including rural and regional areas at some distance to the admitting ICU. Operational reasons[34] and contacting families for prospective consent[35] have been identified as challenges experienced by others and highlight the need for strategies to overcome these barriers when conducting clinical research.

When implementing this intervention across the 3 phases of the study, we identified opportunities to improve the intervention and its delivery. Consistent with the Medical Research Council's guidance on developing and evaluating complex interventions, our modeling of this complex intervention allowed us to modify inclusion criteria used in phases 1 and 2, so that in phase 3, we included all patients who were likely to benefit from improved nutrition during and following recovery from critical illness. Early modeling also informed changes to the timing of intervention delivery, taking into account the need to tailor timing to individual patient and family circumstances. While we continued to aim for recruitment within 48 hours, we were guided by the clinicians' knowledge of the family and extended the possible recruitment period up to 7 days. We were also able to assess the feasibility of intervention delivery by different health professionals and recognized that operational challenges were associated with dietitian availability in some ICUs. Delivery of the intervention by an experienced ICU nurse allowed for more flexibility and the ability to engage with the family during evening visiting hours and could be considered when implementing this intervention in clinical practice or research.

Despite evaluating the feasibility and acceptability of this novel family-centered nutrition intervention in 4 hospitals across 2 countries, we acknowledge that these findings may not be generalizable to all acute care settings. The extent to which an intervention such as the one described in this article can result in improved nutrition intake for patients recovering from critical illness could not be addressed in this feasibility study and requires further investigation.

Conclusion

The consequences of underfeeding and risk for malnutrition are significant and negatively affect patient outcomes, highlighting the need for innovative strategies to improve nutrition intake. A family-centered approach that educates family members of critically ill patients about the importance of nutrition in recovery and encourages them to act as advocates for improved nutrition is feasible and acceptable to families and HCPs in the ICU and on the ward. The next step is to undertake a larger multicenter randomized controlled trial to evaluate the impact of such an intervention on nutrition intake and important patient outcomes.

Statement of Authorship

A. P. Marshall contributed to the conception/design of the research and data analysis and drafted the manuscript; M. Lemieux and R. Dhaliwal contributed to the acquisition, analysis, or interpretation of the data and critically revised the manuscript; H. Seyler and K. N. MacEachern contributed to the acquisition of the data and critically revised the manuscript; and D. K. Heyland contributed to the conception/design of the research and data analysis, and critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

Supplementary Material

Tables S1–S3 are available with the online article at journals.sagepub.com/home/ncp.

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Do Patients With a Baseline Clinical Condition Warranting the Cautious Use of Parenteral Nutrition Develop Subsequent Metabolic Complications?

Diana M. Solomon, PharmD[1]; James M. Hollands, PharmD, BCPS[1,2]; Laura A. Siemianowski, PharmD, BCPS, BCCCP[2]; Colleen E. Smith, PharmD, BCPPS[2]; Richard J. Song, PharmD[2]; and Angela L. Bingham, PharmD, BCPS, BCNSP, BCCCP[1,2]

Abstract

Background: The American Society for Parenteral and Enteral Nutrition Adult Nutrition Support Core Curriculum describes clinical conditions that warrant cautious use of parenteral nutrition (CCWCPN). The Core Curriculum authors acknowledge there is no evidence for specific criteria suggested for the clinical conditions. Consequently, the purpose of this study was to determine the impact of a baseline CCWCPN on the development of subsequent metabolic complications in patients receiving parenteral nutrition (PN). *Methods:* Adult patients initiated on PN from May 2014 to July 2015 at Cooper University Hospital were included in this retrospective study. The impact of a CCWCPN on the development of the following was determined: acid-base disturbances, hepatobiliary complications, hypercapnia, hyperchloremia, hyperglycemia, hypernatremia, hypertriglyceridemia, hypochloremia, hypoglycemia, hypokalemia, hypophosphatemia, and refeeding syndrome. *Results:* Three hundred forty-one patients were included (mean age, 61.7 years; mean duration of PN, 8.5 days; central PN, 97%). Metabolic complications occurred more frequently in patients with a baseline CCWCPN than without these conditions (77% vs 53%, P = .001). Subgroup analyses for the development of metabolic complications in patients with or without each individual baseline CCWCPN yielded the following statistically significant results: hypernatremia (93% vs 57%, P = .007) and hyperchloremia (86% vs 57%, P = .033). *Conclusions:* Hospitalized adult patients with a baseline CCWCPN were more likely to develop a metabolic complication when receiving PN. Baseline hypernatremia and hyperchloremia were associated with the development of metabolic complications. Baseline CCWCPN should be recognized upon initiation of PN; practitioners should closely monitor patients to minimize subsequent metabolic complications. (*Nutr Clin Pract*. 2017;32:400-406)

Keywords

metabolic complications; parenteral nutrition; patient safety; nutrition disorders

Metabolic complications occur more frequently for patients receiving parenteral nutrition (PN) than enteral nutrition (EN); as a result, it is imperative for clinicians to remain vigilant in identifying risk factors for the subsequent development of metabolic complications to minimize their occurrence.[1] Prevention of metabolic complications associated with PN is of utmost importance to clinicians because these complications are associated with adverse patient outcomes. Hyperglycemia, one of the most common metabolic complications from PN documented in the literature, is associated with increased morbidity and mortality.[2–7] Similarly, hypoglycemia is associated with increased complications and mortality.[8–13] In addition, hypercapnia increases respiratory distress and prolongs mechanical ventilation,[14,15] hypertriglyceridemia has been shown to impair lipid clearance and increase the risk of pancreatitis,[16] and refeeding syndrome can result in life-threatening cardiac, pulmonary, gastrointestinal (GI), and neuromuscular complications.[14,17]

When PN is indicated, it should be initiated in patients who are hemodynamically and metabolically stable.[1] Identifying risk factors for the subsequent development of metabolic complications should be an interdisciplinary effort. Healthcare teams should coordinate cohesive plans, closely monitor, and frequently reassess the nutrition needs of at-risk patients to minimize the development of metabolic complications.[15] Despite this guidance for PN management in at-risk patients, objective, evidence-based identification of metabolically unstable patients who are likely to develop a complication is a clinical challenge.

The American Society for Parenteral and Enteral Nutrition (ASPEN) Adult Nutrition Support Core Curriculum authors

From [1]Philadelphia College of Pharmacy, University of the Sciences, Philadelphia, Pennsylvania, USA; and [2]Cooper University Hospital, Camden, New Jersey, USA.

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Corresponding Author:
Angela L. Bingham, PharmD, BCPS, BCNSP, BCCCP, Philadelphia College of Pharmacy, University of the Sciences, 600 S. 43rd St, Philadelphia, PA 19104, USA.
Email: a.bingham@usciences.edu

identify specific criteria that warrant the cautious use of PN; however, these specific criteria are not supported by evidence in the literature.[1] Consequently, the purpose of this study was to determine the impact of a baseline clinical condition warranting cautious use of parenteral nutrition (CCWCPN) on the development of subsequent metabolic complications.

Methods

This study was conducted at Cooper University Hospital, a 600-bed urban academic hospital. Adult patients 18 years of age or older admitted to Cooper University Hospital and initiated on PN from May 2014 to July 2015 were retrospectively evaluated for study inclusion. Patients were excluded if they were <18 years of age, were pregnant, received concomitant EN, or if there was no evaluable laboratory data for any of the baseline CCWCPN. The institutional review boards at Cooper University Hospital and University of the Sciences approved this study.

At this institution, a dietitian consult service in collaboration with physicians, pharmacists, and nurses manages PN without a formal nutrition support team. PN orders are individualized; most often, dietitians are consulted to advise appropriate macronutrient provision prior to PN initiation. Dietitians recommend initiation macronutrient provisions and a time frame for advancing PN to goal. In most instances, 50% of goal intake is provided on day 1 of PN and, if tolerated, patients are advanced to goal intake on day 2 of PN. Through pharmacist collaboration and suggested default electrolytes in the order set, physicians are supported to order appropriate micronutrients.

Glycemic control is managed by the multidisciplinary primary team unless endocrinology is consulted. While this institution lacks a standardized protocol to monitor and treat hyperglycemia in patients receiving PN, most patients are ordered correction scale insulin every 4–6 hours when receiving PN. Insulin is not provided in the PN formulation at this institution.

Study definitions were applied to retrospective review of the electronic medical record (EMR). Investigators applied the specific criteria for baseline CCWCPN as defined by the *A.S.P.E.N. Adult Nutrition Support Core Curriculum*: azotemia (serum urea nitrogen >100 mg/dL), hyperchloremia (chloride >115 mEq/L), hyperglycemia (glucose >300 mg/dL), hypernatremia (sodium >150 mEq/L), hyperosmolality (serum osmolality >350 mOsm/kg), hypochloremia (chloride <85 mEq/L), hypokalemia (potassium <3 mEq/L), and hypophosphatemia (phosphorus <2 mg/dL). A baseline CCWCPN was identified as present if review of laboratory data from 24 hours prior to initiation of PN yielded at least one of the above specified criteria.

Patients were determined to have a subsequent metabolic complication based on the development of any of the following during the PN course of therapy: acid-base disturbances (pH <7.35 or pH >7.45), hepatobiliary complications (documented in the EMR), hypercapnia (pCO_2 >45 mm Hg), hyperchloremia (chloride >115 mEq/L), hyperglycemia (glucose >200 mg/dL), hypernatremia (sodium >150 mEq/L), hypertriglyceridemia (triglycerides ≥400 mg/dL), hypochloremia (chloride <85 mEq/L), hypoglycemia (glucose ≤60 mg/dL), hypokalemia (potassium <3 mEq/L), hypophosphatemia (phosphorus <2 mg/dL), or refeeding syndrome (documented in the EMR). At this institution, PN is initiated at 22:00; accordingly, the first opportunity to document a subsequent metabolic complication was through serum glucose monitoring, which in most patients was initiated within 4 hours of PN initiation and the routine laboratory monitoring the morning (04:00) after the initiation of PN. Some of the subsequent metabolic complications (hepatobiliary complications and refeeding syndrome) were determined to be present in this study based on healthcare team documentation in the EMR that the complication was present during the PN course of therapy. Complete laboratory parameters for evaluation of the development of subsequent metabolic complications were not available for all patients.

Patient demographics and PN characteristics were determined based on a retrospective review of patient EMRs. Some characteristics were determined by calculation; for example, patients were classified by nutrition status by calculating percentage of ideal body weight, creatinine clearance was estimated using the Cockcroft-Gault formula, and infusion rates were calculated by standard dimensional analysis. Infusion rates on day 1 of PN were defined as the rate of infusion of the first PN formulation. It should be noted that day 1 of PN and the term *initiation* are synonymous in this article. Infusion rates at goal were defined as the rate of infusion on the day the patient reached his or her macronutrient goal provision that in most instances was prespecified by a registered dietitian. The Charlson Comorbidity Index, Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores were calculated.[18–20] Patients were determined to be critically ill if they were in the medical/surgical, trauma, or cardiac intensive care unit at the time of PN initiation. Other descriptive characteristics such as active liver disease, diabetes, and congestive heart failure were determined using medical history or diagnoses in the EMR. The organ system of the major diagnosis for the hospitalization was determined based on review of the discharge summary in the EMR.

The primary objective was to determine the impact of a baseline CCWCPN on the subsequent development of metabolic complications. The secondary objective was to determine the impact of each individual baseline CCWCPN on the subsequent development of metabolic complications.

Statistical analysis was performed with SPSS Statistics for Windows, version 23 (SPSS, Inc, an IBM Company, Chicago, IL). Continuous variables that were normally distributed were compared with the unpaired Student *t* test. Continuous data were expressed as mean ± standard deviation (SD). Categorical variables were compared with the χ^2 test or Fisher exact test. Statistical significance was defined as a $P < .05$.

Results

A total of 341 patients were included in the analysis. In the total study population, the mean age was 61.7 years. The mean duration of PN was 8.5 days, and 97% received central PN. Results are listed as patients with a baseline CCWCPN (n = 57) vs patients without a baseline CCWCPN (n = 284) unless otherwise stated. The patients with and without a baseline CCWCPN were similar except for critically ill (49% vs 32%, P = .014), mechanically ventilated (35% vs 18%, P = .011), and diabetes mellitus (37% vs 22%, P = .019). Although the percentage of critically ill and mechanically ventilated patients was greater in the group with a baseline CCWCPN, the 2 groups were similar in their APACHE II, SOFA, and Charlson Comorbidity Index scores. In addition, PN characteristics at initiation were similar for both groups, but they differed in total energy provision and dextrose infusion rates at goal.

A registered dietitian was consulted prior to initiation of PN to advise macronutrient provision in 89% of the patient population; the rate of adherence to dietitian recommendations was 92%. Patients reached goal intake of PN in an average of 2.3 days. Additional patient demographics and PN characteristics are summarized in Table 1.

At least 1 baseline CCWCPN was present in 57 (16%) patients. The baseline CCWCPN for the study population included hypophosphatemia (n = 22), hyperchloremia (n = 14), hypernatremia (n = 14), hypokalemia (n = 13), hyperglycemia (n = 3), azotemia (n = 2), and hypochloremia (n = 2).

Patients with a baseline CCWCPN were more likely to develop a subsequent metabolic complication compared with patients without a baseline clinical condition (77% vs 53%, P = .001). The subgroup analyses to determine the development of any metabolic complications in patients with or without each individual baseline CCWCPN yielded the following statistically significant results (Table 2): hyperchloremia (86% vs 57%, P = .033) and hypernatremia (93% vs 57%, P = .007). Of note, our methods allowed patients with a baseline CCWCPN to subsequently develop the corresponding metabolic complication. However, zero patients with baseline hyperchloremia subsequently developed hyperchloremia, and 1 patient with baseline hypernatremia subsequently developed hypernatremia.

In the total study population, metabolic complications developed in 57% of patients receiving PN. The most common metabolic complications that subsequently developed in patients with a baseline CCWCPN were hyperglycemia (28%), acid-base disturbances (21%), and hypophosphatemia (16%) (Table 3). In patients with a baseline CCWCPN, there were no subsequent instances of hepatobiliary complications, hypercapnia, hypochloremia, hypoglycemia, or refeeding syndrome. The most common metabolic complication in patients without a baseline CCWCPN was hyperglycemia (38%).

Discussion

Nutrition support clinicians must assess a patient's risk for potential complications when initiating PN.[21–24] To aid clinicians in identifying candidates for PN, the *A.S.P.E.N. Adult Nutrition Support Core Curriculum* proposed specific criteria to review[1]; however, this study is the first to support the specific criteria for CCWCPN as defined in the ASPEN resource. Our study demonstrated that patients with a baseline CCWCPN were more likely to subsequently develop a metabolic complication during their PN course. Baseline hypernatremia and hyperchloremia were associated with the development of metabolic complications.

The patient demographics of the 2 study groups were well matched. The 2 groups only differed in the proportion of patients with diabetes mellitus, patients who were critically ill, and patients who were mechanically ventilated. Due to the metabolic instability of patients with diabetes mellitus and critical illness, the investigators anticipated that these patients would present with more baseline CCWCPN. While there were more patients with diabetes mellitus in the group with baseline CCWCPN, only 3 patients presented with hyperglycemia as their CCWCPN. In addition, despite more critically ill and mechanically ventilated patients in the group with a baseline CCWCPN, the predicted mortality risk was similar for both groups based on the mean APACHE II, SOFA, and Charlson Comorbidity Index scores. Other parameters that may reflect severity of illness such as prealbumin, serum albumin, and maximum temperature were not statistically different between the 2 study groups. PN characteristics were also similar between groups and only differed in the total energy provision and dextrose infusion rates at goals. With both groups within an acceptable population-based estimate range of 25–30 kcal/kg/d and well below the maximum rate of glucose utilization, the authors believe these differences may not have been clinically significant.

With metabolic complications occurring in 77% and 53% of patients with and without a baseline CCWCPN, respectively, it is noteworthy that the occurrence of metabolic complications in the group with a baseline CCWCPN is significantly higher than other reports in the literature.[25–27] In a prospective observational study of 100 medical and surgical patients at a university teaching hospital, Weinsier and colleagues[27] observed at least 1 metabolic complication in 63% of patients during PN administration. Weinsier and colleagues[27] observed hyperglycemia (47%), hypophosphatemia (30%), and hypokalemia (18%). A retrospective study by ChrisAnderson and colleagues[25] demonstrated that 55% of patients receiving PN developed a metabolic complication with the most common abnormalities being hyperglycemia (32%) and hypophosphatemia (29%). Last, a retrospective study of PN administration spanning 7 years and including over 2500 patients observed 33% of patients had at least 1 metabolic abnormality. The most common abnormalities included hyperphosphatemia (38%),

Table 1. Patient Demographics and Parenteral Nutrition (PN) Characteristics.[a]

Characteristic	Baseline Clinical Condition Present (n = 57)	Baseline Clinical Condition Not Present (n = 284)	*P* Value
Patient demographics			
Age, y	63.3 ± 17.0	61.3 ± 16.0	.386
Male sex	30 (53)	136 (48)	.513
Race			.620
White	39 (68)	178 (63)	
African American	9 (16)	60 (21)	
Hispanic/Latino	8 (14)	36 (13)	
Nutrition classification			.472
Severe malnutrition, <70% IBW	1 (2)	3 (1)	
Moderate malnutrition, 70–79% IBW	3 (5)	10 (4)	
Mild malnutrition, 80–89% IBW	7 (12)	18 (6)	
Normal, 90–130% IBW	24 (42)	142 (50)	
Obese, >130% IBW	21 (37)	110 (39)	
BMI, kg/m^2	27 ± 7.0	28 ± 9.7	.420
Charlson Comorbidity Index score	3 ± 2.3	3 ± 2.3	1.000
Critically ill	28 (49)	91 (32)	.014
APACHE II score	27 ± 6.6	24 ± 8.8	.205
SOFA score	8 ± 4.4	7 ± 4.8	.392
Mechanically ventilated	20 (35)	56 (18)	.011
CrCl, mL/min	99 ± 72.1	97 ± 63.6	.827
Serum albumin, g/dL[b]	2.5 ± 0.7	2.7 ± 0.8	.092
Prealbumin, mg/dL[c]	8.3 ± 4.4	8.8 ± 5.0	.576
Maximum temperature, °C	37.3 ± 0.6	37.2 ± 0.6	.188
Liver disease	9 (16)	25 (9)	.108
Congestive heart failure	3 (5)	17 (6)	.832
Diabetes mellitus	21 (37)	63 (22)	.019
Organ system of major diagnosis			
Cardiovascular	4 (7)	15 (5)	.602
Gastrointestinal	39 (68)	207 (73)	.492
Endocrine	4 (7)	11 (4)	.291
Lymphatic and immune	1 (2)	5 (2)	.997
Nervous	1 (2)	2 (1)	.438
Reproductive	1 (2)	8 (3)	.648
Respiratory	4 (7)	13 (5)	.440
Urinary	0	16 (6)	.066
PN characteristics			
Indication for PN			
Bowel obstruction	11 (19)	50 (18)	.761
Failure to achieve enteral goals	8 (14)	40 (14)	.992
Gut ischemia	1 (2)	4 (1)	.843
Ileus	4 (7)	18 (6)	.849
Inaccessible gastrointestinal tract	13 (23)	68 (24)	.854
Intolerance to enteral feeding	4 (7)	28 (10)	.502
Other	10 (18)	56 (20)	.705
Refractory diarrhea and or vomiting	5 (9)	17 (6)	.435
Short bowel syndrome	1 (2)	3 (1)	.656
Consecutive days of PN	8 ± 5.6	9 ± 9.8	.555
Central PN	54 (95)	278 (98)	.176
Protein provision on day 1 of PN, g/kg/d	1.46 ± 0.42	1.47 ± 0.33	.832
Energy provision (nonprotein and protein calories) on day 1 of PN, kcal/kg/d	18 ± 5.3	19 ± 4.2	.419

(continued)

Table 1. (continued)

Characteristic	Baseline Clinical Condition Present (n = 57)	Baseline Clinical Condition Not Present (n = 284)	*P* Value
Dextrose infusion on day 1 of PN, mg/kg/min	1.50 ± 0.72	1.51 ± 0.56	.901
Lipid infusion rate on day 1 of PN, g/kg/d	0.39 ± 0.20	0.41 ± 0.17	.385
Protein provision at goal, g/kg/d	1.68 ± 0.66	1.59 ± 0.50	.260
Energy provision (nonprotein and protein calories) at goal, kcal/kg/d	28 ± 8.0	27 ± 7.5	.040
Dextrose infusion at goal, mg/kg/min	2.60 ± 0.87	2.39 ± 0.94	.045
Lipid infusion rate at goal, g/kg/d	0.71 ± 0.28	0.70 ± 0.29	.489
Glycemic control characteristics			
No. of hyperglycemic events 24 hours prior to initiation (serum glucose >200 mg/dL)	0.42 ± 1.11	0.22 ± 0.76	.092
Insulin requirement 24 hours prior to initiation, units	5.4 ± 14.7	2.8 ± 16.8	.289
No. of hyperglycemic events 24 hours after initiation (serum glucose >200 mg/dL)	0.86 ± 1.67	0.76 ± 1.75	.683
Insulin requirement 24 hours after initiation, units	11.5 ± 25.2	6.62 ± 29.6	.244

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CrCl, creatinine clearance estimated using Cockcroft-Gault; Critically ill, patient location in medical/surgical, trauma, or cardiac intensive care units at PN initiation; IBW, ideal body weight; SOFA, Sequential Organ Failure Assessment.
[a]Data are listed as mean ± SD or n (%).
[b]Serum albumin available for n = 52 and n = 244 patients for baseline condition present and absent, respectively.
[c]Prealbumin available for n = 36 and n = 181 patients for baseline condition present and absent, respectively.

Table 2. Impact of Each Baseline Clinical Condition Warranting the Cautious Use of Parenteral Nutrition on the Development of a Subsequent Metabolic Complication.

	Development of Any Subsequent Metabolic Complication		
Baseline Clinical Condition	Baseline Condition Present, a/b (%)	Baseline Condition Not Present, x/y (%)	*P* Value
Azotemia	1/2 (50)	186/320 (58)	.816
Hyperchloremia	12/14 (86)	175/307 (57)	.033
Hyperglycemia	2/3 (67)	185/319 (58)	.762
Hypernatremia	13/14 (93)	174/307 (57)	.007
Hyperosmolality	0 (0)	187/321 (58)	—
Hypochloremia	2/2 (100)	185/319 (58)	.230
Hypokalemia	10/13 (77)	177/308 (57)	.164
Hypophosphatemia	17/22 (77)	146/258 (57)	.059

a, number of patients who developed any subsequent metabolic complication if a baseline condition was present; b, total number of patients with the baseline condition; x, number of patients who developed any subsequent metabolic complication if a baseline condition was not present; y, total number of patients without the baseline condition.

hyponatremia (33%), hyperkalemia (30%), and hyperglycemia (28%).[26]

Similar to the previous literature, hyperglycemia was the most common metabolic complication in our patients with a baseline CCWCPN (28%). Interestingly, hyperglycemia developed in a higher percentage of patients without a baseline CCWCPN (38%), even though there were more patients who were critically ill and with diabetes mellitus in the group with a baseline CCWCPN. Also, the dextrose infusion rate was higher in the group with a baseline CCWCPN. It is of note that patients without a baseline CCWCPN received less insulin than patients with a baseline CCWCPN, but this trend was not statistically significant. These hyperglycemia rates may be due to the large percentage of patients who were critically ill (35%) and with diabetes mellitus (25%) in the total study population. In addition, the study population was older, with a mean age of 61.7 years. The oxidation rate for dextrose is reduced for hypermetabolically stressed critically ill patients, patients with diseases that alter the effects of insulin such as diabetes mellitus, and elderly patients.[28,29] Moreover, this institution lacks a standardized protocol to monitor and treat hyperglycemia in patients receiving PN, which could explain the high proportion

Table 3. Metabolic Complications That Subsequently Developed in Patients Receiving Parenteral Nutrition (PN) With a Baseline Clinical Condition Warranting the Cautious Use of PN.

Metabolic Complication	Patients With a Baseline Clinical Condition, No. (%) (n = 57)
Hyperglycemia	16 (28)
Acid-base disturbances	12 (21)
Hypophosphatemia	9 (16)
Hyperchloremia	5 (9)
Hypertriglyceridemia	4 (7)
Hypernatremia	2 (4)
Hypokalemia	2 (4)

of patients developing hyperglycemia in the total population. In both groups, the dextrose infusion rate was conservatively initiated at a mean <2 mg/kg/min.

It is noteworthy that our methods allowed patients with a baseline CCWCPN to subsequently develop the corresponding metabolic complication. We do not believe this affected our results, as zero patients with baseline hyperchloremia subsequently developed hyperchloremia, and 1 patient with baseline hypernatremia subsequently developed hypernatremia. Authors also reviewed attempted correction of electrolytes upon initiation of PN. We observed 8 instances of hypokalemia receiving intravenous (IV) boluses of potassium chloride, 14 instances of hypophosphatemia receiving either IV boluses of potassium phosphorus or sodium phosphorus or both, and 1 instance of hypochloremia receiving an IV bolus of potassium chloride. As described above, there was only 1 instance where the baseline clinical condition was not corrected before PN initiation.

This study supports the *A.S.P.E.N. Adult Nutrition Support Core Curriculum* definitions of the specific criteria for CCWCPN. Consequently, clinicians and institutions may incorporate the CCWCPN into their assessment strategies for patients receiving PN. First, the CCWCPN may be incorporated into policies and procedures for PN management. The ASPEN Parenteral Nutrition Safety Consensus Recommendations emphasize the complexity of PN therapy; standardized procedures are crucial to minimize the frequency and severity of PN-associated complications.[30,31] In addition, literature has demonstrated that when current standards are followed, PN does not contribute to more complications than EN.[32,33] Evaluation of baseline laboratory values and identification of CCWCPN may be incorporated into procedures such that ordering prescribers and other members of the interdisciplinary team are aware of baseline risk factors that increase the likelihood of the development of metabolic complications. Second, consideration of baseline CCWCPN can facilitate appropriate initiation of macronutrients and micronutrients and prompt subsequent monitoring to ensure patients are metabolically stable and avoid potential negative outcomes associated with PN therapy. Finally, the CCWCPN can be incorporated into the regular competencies and assessments of interdisciplinary healthcare professionals who manage PN to raise and maintain awareness of these conditions that contribute to complications.[34,35]

Several limitations were identified in this study. Since this was a retrospective study, the occurrence of subsequent metabolic complications may have been underreported for complications that investigators relied on documentation in the EMR by the medical team. Also, we may have underreported the development of metabolic complications because laboratory parameters were not always available to assess the development of all possible metabolic complications. For example, blood gasses were only routinely available in mechanically ventilated critically ill patients. In addition, it is possible that subsequent metabolic complications may have occurred because of confounders not included in our study. Furthermore, the clinical significance of subsequent metabolic complications was not evaluated in this study. The small number of patients presenting with some of the baseline CCWCPN could have prohibited our ability to demonstrate statistical significance in their individual impact on the development of subsequent metabolic complications. Moreover, the presence of baseline CCWCPN could have been undercollected because laboratory parameters were not always available to assess all baseline conditions. Investigators did not account for the presence of more than 1 baseline CCWCPN and did not evaluate the relationship between each CCWCPN and each subsequent metabolic complication; future studies may evaluate these areas. Since this study was conducted in adult hospitalized patients, results may not apply to long-term care facility or home PN patients.

Conclusion

Hospitalized adult patients with a baseline CCWCPN, as defined by the ASPEN Core Curriculum for Adult Patients, are more likely to subsequently develop a metabolic complication during their PN course. Baseline hypernatremia and hyperchloremia are associated with the development of metabolic complications. The low occurrence of baseline conditions warranting cautious use of PN may have limited our ability to demonstrate a statistically significant impact of other individual criteria. Baseline CCWCPN should be recognized upon initiation of PN and prompt practitioners to closely monitor patients to minimize subsequent metabolic complications.

Statement of Authorship

D. M. Solomon and A. L. Bingham contributed to the acquisition of data and drafted the manuscript; and all authors contributed to the conception or design, contributed to data analysis or interpretation, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Retrospective Dual-Center Study of Parenteral Nutrition–Associated Cholestasis in Premature Neonates: 15 Years' Experience

Weihui Yan, PhD, MD[1,2,3*]; Li Hong, PhD, MD[4*]; Ying Wang, PhD, MD[1,2,3*]; Yi Feng, PhD, MD[4]; Lina Lu, MD[1,2,3]; Yijing Tao, MD[1,2,3]; Jiang Wu, PhD, MD[1,2,3]; Huijuan Ruan, MD[1,2,3]; Qingya Tang, PhD, MD[1,2,3]; and Wei Cai, PhD, MD[1,2,3,5]

Abstract

Background: The pathogenesis of parenteral nutrition–associated cholestasis (PNAC) has not been clarified. The objective of this study was to explore the incidence of PNAC in premature infants without surgery and to identify associated risk factors. *Materials and Methods:* Premature neonates who received parenteral nutrition (PN) at least 14 days were included in a retrospective, dual-center study. Cholestasis was diagnosed as conjugated bilirubin ≥2 mg/dL. Infants with metabolic liver disease, cyanotic congenital heart disease, congenital syphilis, hepadnaviridae infection, and those who underwent surgery were excluded. Infants were divided into 3 groups chronologically: group A (2000–2004, n = 50), group B (2005–2009, n = 283), and group C (2010–2014, n = 741). A case-controlled study was conducted by comparing infants with PNAC to those without PNAC. *Results:* Of 1074 premature neonates, PNAC was confirmed in 53 infants (4.93%). There were 6.8% very low birth weight (BW) infants and 20.0% extremely low BW infants who developed PNAC. The incidence of PNAC decreased slightly during 2000–2014 (8.0%, 6.4%, and 4.2% in groups A, B, and C, respectively). Compared with those without PNAC, infants with PNAC (n = 53) had significantly younger gestational age, lower BW, longer PN duration, and higher rate of sepsis. Logistic regression showed male sex, PN duration ≥43 days, and sepsis were statistically correlated with PNAC. *Conclusions:* Prolonged duration (≥43 days), male sex, and sepsis are probably independent risk factors for developing PNAC in premature neonates. (*Nutr Clin Pract*. 2017;32:407-413)

Keywords

parenteral nutrition; cholestasis; premature infant; risk factors; nutrition support

Parenteral nutrition (PN) has become an essential measure for neonates, especially premature and low birth weight infants who are unable to sustain adequate growth by enteral feeding. Parenteral nutrition–associated cholestasis (PNAC) is a major complication of PN in neonates and one of the most challenging problems for neonatal practitioners.[1] PNAC pathogenesis may be multifactorial, and a number of risk factors have been recognized to be attributed to PNAC, such as prolonged administration of PN, low birth weight (BW), prematurity, severe infections, PN components, total caloric overloading, enzyme deficiencies, genetic causes, anatomic factors, absence of enteral feeding, small for gestational age, male sex, and intestinal resection.[1–13]

It has been reported that the overall incidence of PNAC is 28.2% in children receiving PN for ≥14 days.[1] Although several advancements in prolonged PN treatment have been made over the past decades, such as improvements in PN components by addition of fish oil and reductions in ω-6 fatty acid (linoleic acid) and aseptic catheter placement techniques,[13] there has been no obvious decrease in PNAC incidence over the past 40 years.[1]

The aim of this study was to describe PN practices exclusively in premature neonates without surgery at 2 centers in the

From the [1]Department of Clinical Nutrition, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Shanghai Institute of Pediatric Research, Shanghai, China; [3]Shanghai Key Laboratory of Pediatric Gastroenterology and Nutrition, Shanghai, China; [4]Department of Clinical Nutrition, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; and the [5]Department of Pediatric Surgery, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

*These authors contributed equally to this work and share first authorship.

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Corresponding Author:
Wei Cai, PhD, MD, Department of Clinical Nutrition, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, No. 1665, Kong Jiang Road, Shanghai, China.
Email: caiw1978@163.com

People's Republic of China from January 2000 to December 2014 and to explore potential risk factors for developing PNAC during the neonatal period to suggest possible methods of prevention for decreasing PNAC incidence.

Materials and Methods

Study Design

This was a retrospective, dual-center study. It was granted for access to patient files by the Research Ethical Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. We reviewed the medical records of premature neonates who were admitted to the neonatal intensive care unit (NICU) and received PN at Xin Hua Hospital and Shanghai Children's Medical Center from January 2000 to December 2014.

Patients and Definitions

The inclusion criteria were (1) gestational age (GA) <37 weeks, (2) PN maintained at least 14 days, and (3) infants who were admitted to NICU before the age of 7 days. Infants were excluded if they had the following: (1) metabolic liver disease, (2) cyanotic congenital heart disease, (3) congenital syphilis, (4) hepadnaviridae infection, (5) direct bilirubin (D.Bil) level ≥2 mg/dL at baseline, and (6) if they had undergone surgery.

Of all infants who met inclusion criteria (n = 1074), 50 cases received PN during 2000–2004 (group A), 283 cases during 2005–2009 (group B), and 741 cases throughout 2010–2014 (group C). The PN solution consisted of lipids (20% medium-chain triglyceride [MCT]/long-chain triglyceride [LCT] emulsions; B. Braun, Melsungen, Hessen, Germany), amino acids (6% pediatric amino acids; CR Pharmaceutical, Beijing, China), glucoses, minerals, trace elements, and water-soluble and fat-soluble vitamins. The amount of PN was subsequently decreased when enteral intake increased. Clinical information included GA, BW, sex, sepsis, age at PN initiation, age at introduction of enteral nutrition (EN), days of PN with EN, and PN duration. We also recorded PN calories and dose of amino acids, glucose, and lipids used for the longest period of time. Liver function tests, including bilirubin levels, were measured at baseline and then weekly thereafter. Cholestasis was diagnosed when the conjugated bilirubin was ≥2 mg/dL.[1,14–16] Confirmed sepsis was defined as positive blood culture.

Statistical Analysis

Data were analyzed using SPSS 19.0 for Windows (SPSS, Inc, an IBM Company, Chicago, IL). Continuous variables, which are presented as median (interquartile range [IQR]) or mean ± standard deviation (SD), were compared using a Mann-Whitney nonparametric test or Student *t* test between 2 groups. We carried out a Kruskal-Wallis nonparametric test to determine the differences among 3 groups. Categorical data were compared by χ^2 test and odds ratio (OR). A *P* value <.05 was considered statistically significant. Potential risk factors associated with PNAC in univariate analyses at a *P* value <.10 were further tested using multivariate binary logistic regression.

Results

Of 1074 premature neonates who met the study criteria, PNAC was confirmed in 53 infants as the PNAC group. None developed irreversible fatal liver cirrhosis. The remaining 1021 infants served as the non-PNAC group. PNAC incidence was 4.93%, 6.8%, and 20.0% in all premature neonates, very low BW infants, and extremely low BW infants, respectively.

PNAC Incidence Trends Throughout the Decades

The incidence of PNAC has declined from 8.0% (group A, 2000–2004) to 4.2% (group C, 2010–2014) chronologically over past decades (Table 1). Meanwhile, sepsis has declined from 52.0% to 5.1% (*P* < .001). During the past 15 years, we have tended to increase PN calories and dose of amino acids and glucose (*P* < .001) and introduce EN and PN earlier (*P* < .001). BW, GA, and male sex did not show significant differences among 3 groups.

Potential Risk Factors Associated With PNAC

Comparing the PNAC group with the non-PNAC group (Table 2), neonates with PNAC had significantly younger GA (30.1 [28.7–32.1] weeks vs 31.7 [30.1–33.1] weeks; *P* < .001) and lower BW (1260 [1084–1508] g vs 1550 [1340–1816] g; *P* < .001). They also had longer PN duration (29 [20–43] days vs 19 [16–25] days; *P* < .001) and higher rate of sepsis (22.6% vs 5.8%; odds ratio [OR], 4.772; 95% CI, 2.382–9.561; *P* < .001). A higher ratio of male sex was observed in neonates with PNAC but without statistical significance (male, 71.7% vs 59.3%; OR, 1.742; 95% CI, 0.946–3.208; *P* = .072). There were no significant differences with respect to other factors, including age at PN initiation, age at EN introduction, PN calories, or dose of PN components using the nonparametric test between 2 groups. However, we further carried out subgroup analysis and found that infants who received PN with lipids >2.0 g/kg/d (*P* = .004), amino acids >3.5 g/kg/d (*P* = .034), or calories >90 kcal/kg/d (*P* = .010) were more likely to develop PNAC, as shown in Table 3.

After univariate analysis, 8 factors including sepsis, sex, PN duration, BW, GA, PN calories, dose of lipids, and amino acids were selected for further analysis. Multivariate binary logistic

Table 1. Characteristics of Premature Infants Over Different Time Periods.

Characteristic	Group A, 2000–2004 (n = 50)	Group B, 2005–2009 (n = 283)	Group C, 2010–2014 (n = 741)	*P* Value			
				Overall	A vs B	A vs C	B vs C
PNAC, No. (%)	4 (8.0)	18 (6.4)	31 (4.2)	.210			
Gestational age, median (IQR), weeks	31.5 (30.3–32.4)	31.7 (30.0–33.0)	31.6 (30.0–33.3)	.792			
Birth weight, median (IQR), g	1515 (1318–1818)	1563 (1394–1801)	1530 (1300–1800)	.220			
Sex, male, No./total No. (%)	28/50 (56.0)	167/283 (59.0)	448/741 (60.5)	.777			
Duration of PN, median (IQR), days	19 (15–27)	18 (15–23)	20 (16–27)	.001	.287	<.001	.475
Age at PN initiation, median (IQR), days	4 (3–5)	3 (2–4)	2 (1–3)	<.001	<.001	<.001	<.001
Age at EN introduction, median (IQR), days	6 (3–9)	6 (3–11)	3 (2–4)	<.001	.237	<.001	<.001
Days of PN with EN, median (IQR)	15 (12–23)	16 (13–17)	19 (15–26)	.010	.484	.009	.098
Lipids, median (IQR), g/kg/d	1.5 (1.0–2.0)	1.5 (1.0–2.0)	1.6 (1.3–2.0)	.157			
Amino acids, median (IQR), g/kg/d	2.0 (1.7–2.1)	2.6 (2.0–3.0)	2.8 (2.2–3.3)	<.001	<.001	<.001	<.001
Glucose, median (IQR), g/kg/d	7.4 (6.1–8.9)	8.7 (6.5–10.0)	9.6 (7.3–12.0)	<.001	.084	<.001	<.001
PN calories, median (IQR), kcal/kg/d	52.8 (46.8–60.1)	61.8 (47.3–70.6)	65.7 (53.0–77.0)	<.001	.005	<.001	<.001
Weight gain, median (IQR), g/kg/d	16.4 (11.6–23.1)	11.5 (7.8–17.7)	15.7 (10.0–20.7)	<.001	<.001	.103	<.001
Sepsis, No. (%)	26 (52.0)	7 (2.5)	38 (5.1)	<.001	<.001	<.001	.064

EN, enteral nutrition; IQR, interquartile range; PN, parenteral nutrition; PNAC, parenteral nutrition–associated cholestasis.

Table 2. Characteristics of Premature Infants With and Without Parenteral Nutrition–Associated Cholestasis (PNAC).

Characteristic	PNAC (n = 53)	Non-PNAC (n = 1021)	*P* Value
Sex, male, No. (%)	38 (71.7)	605 (59.3)	.072
Gestational age, median (IQR), weeks	30.1 (28.7–32.1)	31.7 (30.1–33.1)	<.001[a]
Birth weight, median (IQR), g	1260 (1084–1508)	1550 (1340–1816)	<.001[a]
Duration of PN, median (IQR), days	29 (20–43)	19 (16–25)	<.001[a]
Age at PN initiation, median (IQR), days	2 (1–4)	2 (1–3)	.679
Age at EN introduction, median (IQR), days	3 (1–7)	3 (2–5)	.681
PN with EN, median (IQR), days	24 (19–34)	18 (14–25)	.004[a]
Lipids, mean ± SD, g/kg/d	1.7 ± 0.6	1.6 ± 0.5	.219
Amino acids, mean ± SD, g/kg/d	2.8 ± 0.8	2.6 ± 0.7	.039[a]
Glucose, mean ± SD, g/kg/d	9.9 ± 2.6	9.1 ± 3.0	.075
PN calories, mean ± SD, kcal/kg/d	67.6 ± 16.7	62.8 ± 16.1	.035[a]
Weight gain, median (IQR), g/kg/d	11.8 (8.4–18.2)	14.8 (9.3–20.0)	.134
Sepsis, No. (%)	12 (22.6)	59 (5.8)	<.001[a]

EN, enteral nutrition; IQR, interquartile range; PN, parenteral nutrition.
[a]$P < .05$.

regression modeling showed that male sex (OR, 2.342; 95% CI, 1.149–4.773; $P = .019$), PN duration ≥43 days (OR, 7.757; 95% CI, 2.867–20.986; $P < .001$), and sepsis (OR, 3.657; 95% CI, 1.585–8.436; $P = .002$) were statistically correlated to PNAC (Table 4). Other factors, by contrast, were not accepted as independent risk factors in this model.

Table 3. Subgroup Analysis in Infants With and Without Parenteral Nutrition–Associated Cholestasis (PNAC).

Variable	PNAC (n = 53)	Non-PNAC (n = 1021)	OR (95% CI)	*P* Value
Gestational age, weeks, No. (%)[a]				<.001[b]
<30	24 (47.1)	195 (19.4)	1	
30 to <32	14 (27.5)	348 (34.6)	0.327 (0.165–0.647)	.001[b]
32 to <34	8 (15.7)	270 (26.9)	0.241 (0.106–0.547)	<.001[b]
34 to <37	5 (9.8)	192 (19.1)	0.212 (0.079–0.566)	.001[b]
Birth weight, g, No. (%)[a]				<.001[b]
<1000	7 (14.0)	28 (2.8)	1	
1000 to <1500	29 (58.0)	398 (39.4)	0.291 (0.117–0.724)	.013[b]
1500 to <2500	13 (26.0)	555 (55.0)	0.094 (0.035–0.253)	<.001[b]
≥2500	1 (2.0)	29 (2.9)	0.138 (0.016–1.194)	.060
Duration of PN, days, No. (%)				<.001[b]
14–28	25 (47.2)	841 (82.4)	1	
29–42	15 (28.3)	145 (14.2)	3.480 (1.792–6.760)	<.001[b]
≥43	13 (24.5)	35 (3.4)	12.497 (5.898–26.469)	<.001[b]
Lipids, g/kg/d, No. (%)[a]				
≤2.0	36 (69.2)	859 (84.3)	1	.004[b]
>2.0	16 (30.8)	160 (15.7)	2.386 (1.293–4.403)	
Amino acids, g/kg/d, No. (%)[a]				
≤3.5	45 (84.9)	949 (93.5)	1	.034[b]
>3.5	8 (15.1)	66 (6.5)	2.556 (1.157–5.646)	
Glucose, g/kg/d, No. (%)[a]				
≤12	39 (76.5)	824 (81.3)	1	.386
>12	12 (23.5)	189 (18.7)	1.341 (0.689–2.611)	
PN calories, kcal/kg/d, No. (%)[a]				
≤90	46 (88.5)	979 (96.5)	1	.010[b]
>90	6 (11.5)	35 (3.5)	3.648 (1.461–9.110)	

OR, odds ratio; PN, parenteral nutrition.
[a]The specific information of some infants was missing.
[b]$P < .05$.

Table 4. Logistic Regression Test (n = 1033).

Variable	OR	95% CI	*P* Value
Gestational age, weeks			.998
≥34	1		
32 to <34	1.078	0.321–3.623	.903
30 to <32 w	1.002	0.310–3.231	.998
<30	1.066	0.293–3.879	.923
Birth weight, g			.219
≥2500	1		
1500 to <2500	0.770	0.083–7.169	.818
1000 to <1500	1.500	0.151–14.900	.729
<1000	2.914	0.233–36.447	.407
Duration of PN, days			<.001[a]
14–28	1		
29–42	2.128	0.962–4.707	.062
≥43	7.757	2.867–20.986	<.001[a]
Sex, male	2.342	1.149–4.773	.019[a]
Sepsis	3.657	1.585–8.436	.002[a]
Lipids	1.763	0.803–3.870	.157
Amino acids	1.596	0.465–5.475	.458
PN calories	1.275	0.291–5.592	.747

OR, odds ratio; PN, parenteral nutrition.
[a]$P < .05$.

Discussion

PNAC is a recognized predictor of mortality and significantly life-threatening events in infants on long-term PN[17]; its etiology is not well understood. Despite several risk factors being proposed, there are controversies over whether some are independent factors, such as small for GA,[3,6,10] low BW,[18,19] young GA,[2,7,19–21] and male sex.[2,10,22] In this retrospective study, after univariate analyses, sepsis, male sex, longer PN duration, lower BW, younger GA, more daily calorie intake, and higher dose of lipids and amino acids were indicated to be potentially associated with PNAC. However, the logistic regression model shows that some of the factors, including BW and GA, are probably not independently associated with PNAC.

Some studies have reported that surgical disorders are strongly associated with developing PNAC.[5,6,18] Thus, we excluded surgery infants to focus on other factors. The overall incidence of PNAC was only 4.93% in premature neonates in this study, much lower than previous reports.[1,2,15,23,24] Several causes might contribute to this discrepancy. First, our infants received a lower administration of lipids (1.5 [1.2–2.0] g/kg/d), glucose (9.0 [7.0–11.4] g/kg/d), amino acids (2.7 [2.1–3.2] g/kg/d), and PN calories (63.7 [51.6–74.9] kcal/kg/d), compared with the amounts reported to be associated

with the development of PNAC.[2,9,11,25,26] Next, we administered an amino acid formula containing taurine, which was suggested to significantly reduce PNAC in infants with necrotizing enterocolitis.[7] Then, the median BW was lower and median PN duration was shorter in our population compared with previous reports.[10,15,18] Finally, we excluded infants who underwent surgery, which has been previously demonstrated to be associated with PNAC.[5,6,18] On the other hand, endeavors of the nutrition support team (NST), which was established in 1995, should not be neglected in this respect. The NST prescribed individualized PN and EN to infants and implemented daily ward rounds to facilitate adjustments to changes of clinical status.

GA, BW, and PN Duration

GA, BW, and PN duration are difficult to be precisely separated because premature and low BW infants likely require longer PN. Plenty of cases have demonstrated that prematurity and low BW are risk factors for PNAC.[5,6,10–12,18,19] However, several researchers have raised questions as to whether prematurity or low BW is an independent risk factor for PNAC.[2,5,7,19] For instance, no relationship between prematurity and PNAC was shown by a multiple regression model in a prospective trial.[7] In another study,[19] infants with PNAC showed significantly lower BW and younger GA, but they failed to reveal a statistically significant association by multivariate analysis.

Our data suggest that low BW and young GA are not statistically correlated to PNAC by logistic regression among premature infants treated with PN for at least 14 days, whereas prolonged PN duration (≥43 days) is identified as an independent risk factor for PNAC, in accordance with the report by Hsieh et al.[19]

Dose of PN Components

Some data suggest that PN overfeeding is implicated in the development of PNAC.[27] Shin et al[25] showed that cumulative lipid infusion contributes to the development of PNAC. It was reported that an increase from baseline for conjugated bilirubin and total bile acids total was reduced in the lower dose of lipids group.[28] Jolin-Dahel et al[2] found that the PNAC group received a higher dose of carbohydrates (14.4 vs 12 g/kg/d; $P = .02$), indicating high carbohydrate content as a risk factor for developing PNAC. Vileisis et al[26] randomized 82 infants to receive PN with protein intakes averaging 2.3 or 3.6 g/kg/d. The prospective controlled study found that an increased protein intake was associated with earlier and more severe PNAC, and those with PNAC were exposed to significantly higher concentrations of dextrose in their PN solutions compared with those who did not.

In this study, infants who received PN with lipids >2.0 g/kg/d ($P = .004$), amino acids >3.5 g/kg/d ($P = .034$), or calories >90 kcal/kg/d ($P = .010$) were inclined to develop PNAC, but none was identified as independent risk factor for PNAC in a logistic regression model. It was noticed that the daily calorie intake, dose of amino acids, and glucose increased significantly ($P < .001$) while the incidence of PNAC decreased through past decades. We presumed that PN calorie intake, dose of glucose, and amino acids used in appropriate ranges may not be major contributors to PNAC, while dose of lipids would have more effects on PNAC. However, most infants received partial PN in this study, and the dose of components we analyzed was administrated for the longest period (not maximal dose). Because most data for EN were missing in this retrospective study, we just analyzed EN calorie and total calorie intake in 52 infants. Their EN calorie intake was 51.8 ± 19.5 kcal/kg/d, and total calorie intake was 103.7 ± 15.4 kcal/kg/d. Dose of parenteral components was adjusted according to EN intake to meet adequate nutrient requirements and avoid growth retardation. We suggest that promoting EN (not lipid minimization) is an advisable measure to decrease the incidence of PNAC.

Sepsis

Sepsis has been recognized as a risk factor for PNAC for decades.[4,5,19] Robinson and Ehrenkranz[6] showed that infants with PNAC had a higher proportion of sepsis (80% vs 34%), and Beath et al[20] also demonstrated that sepsis episodes were associated with a 30% increase in bilirubin levels in infants undergoing surgery. Furthermore, it was reported that gram-negative septicemia played a significant role in contributing to PNAC in neonates who had percutaneously inserted central catheters used for PN by multivariate logistic analysis.[29]

Consistently, we found a higher proportion of sepsis in premature neonates with PNAC compared with those without PNAC (22.6% vs 5.8%; $P < .001$). Multivariate logistic analysis further revealed that sepsis was recognized as a risk factor for PNAC. We speculated that the reduction of sepsis might be a major reason for decreases in PNAC incidence over the past 15 years. This study is retrospective, so we could not get the precise reason for the high incidence of sepsis in group A. We supposed that it was associated with the poor aseptic practice before 2005 and partly because of the small denominator. Compared with other groups, the total number of patients was very few in group A, perhaps because of fewer NICU beds, lower proportion of preterm infants who received PN, and higher proportion of preterm infants who dropped out of therapy before 2005. Future studies will explore how to decrease the incidence of sepsis in preterm infants.

Sex

The idea of sex differences in PNAC has not yet reached a consensus among researchers. For instance, Albers et al[22] showed that male sex may predispose neonate surgical patients to PNAC, and similar results were reported by Jolin-Dahel et al.[2] However, male sex is not identified as a risk factor in many other studies.[3,8,10,30]

Our study showed the percentage of boys was higher in the PNAC group than the non-PNAC group (71.7% vs 59.3%; P = .072), and multivariate logistic regression identified male sex as an independent risk factor for PNAC. The underlying mechanism behind this relationship has not yet been clearly demonstrated. Albers et al[22] found a correlation between sepsis and sex; however, our analysis was inconsistent with their results (OR, 1.251; 95% CI, 0.757–2.069; P = .382). Animal studies have suggested that the male sex steroid testosterone or low levels of female sex steroids may attribute to a detrimental immunological effect,[22] but it has not been shown whether this immunological defect helps or hinders PNAC development.

Strengths and Limitations

The strengths of our study included the large sample size and the dual-center study design. The sample size was quite large, so we had sufficient statistical power to detect potential factors associated with PNAC. Second, the PN solutions were all prescribed by the NST, decreasing the effect of disparity in knowledge. Furthermore, we excluded some potential confounded factors by defining the inclusion and exclusion criteria.

However, we do acknowledge a limitation was its retrospective design. The factors analyzed were uncontrolled, and the results were unavoidably confounded. In addition, many data about EN were missing, so we just analyzed EN calorie and total calorie intake in 52 infants. Finally, the sample before 2005 was very small, so the calculated incidence might not be accurate because of the small denominator.

Conclusions

PNAC was more common in premature male neonates with sepsis and prolonged PN duration (≥43 days). Learning from our experience, several measures to limit PNAC can be suggested, such as avoiding overfeeding, decreasing sepsis, withdrawing PN as soon as possible, and individualized nutrition therapy administered by the NST.

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Statement of Authorship

W. Cai, Q. Tang, L. Hong, W. Yan, and Y. Wang equally contributed to the conception and design of the research; L. Lu and Y. Tao contributed to the design of the research; W. Yan, Y. Wang, H. Ruan, and J. Wu contributed to the acquisition of the data; W. Yan, L. Lu, and Y. Tao contributed to the analysis of the data; and W. Cai, W. Yan, and Y. Wang contributed to the interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Energy and Protein Delivery in Overweight and Obese Children in the Pediatric Intensive Care Unit

Enid E. Martinez, MD[1,2]; Katelyn A. Ariagno, RD[3]; Nicole Stenquist, BA[1]; Daniela Anderson, MD[4]; Eliana Muñoz, MD[5]; and Nilesh M. Mehta, MD[1,2,3]

Abstract

Background: Early and optimal energy and protein delivery have been associated with improved clinical outcomes in the pediatric intensive care unit (PICU). Overweight and obese children in the PICU may be at risk for suboptimal macronutrient delivery; we aimed to describe macronutrient delivery in this cohort. *Methods:* We performed a retrospective study of PICU patients ages 2–21 years, with body mass index (BMI) ≥85th percentile and >48 hours stay. Nutrition variables were extracted regarding nutrition screening and assessment, energy and protein prescription, and delivery. *Results:* Data from 83 patient encounters for 52 eligible patients (52% male; median age 9.6 [5–15] years) were included. The study cohort had a longer median PICU length of stay (8 vs 5 days, $P < .0001$) and increased mortality rate (6/83 vs 182/5572, $P = .045$) than concurrent PICU patient encounters. Detailed nutrition assessment was documented for 60% (50/83) of patient encounters. Energy expenditure was estimated primarily by predictive equations. Stress factor >1.0 was applied in 44% (22/50). Median energy delivered as a percentage of estimated requirements by the Schofield equation was 34.6% on day 3. Median protein delivered as a percentage of recommended intake was 22.1% on day 3. *Conclusions:* The study cohort had suboptimal nutrition assessments and macronutrient delivery during their PICU course. Mortality and duration of PICU stay were greater when compared with the general PICU population. Nutrition assessment, indirect calorimetry-guided energy prescriptions, and optimizing the delivery of energy and protein must be emphasized in this cohort. The impact of these practices on clinical outcomes must be investigated. (*Nutr Clin Pract*. 2017;32:414-419)

Keywords

obesity; critical care; pediatrics; nutrition; energy; protein; intensive care unit; nutrition assessment; energy expenditure; mortality

Obesity is prevalent in the pediatric intensive care unit (PICU) and has been associated with a higher risk for morbidity and mortality.[1–6] Nutrition guidelines for the pediatric critically ill patient recommend early and frequent nutrition assessments, as well as indirect calorimetry for measurement of energy expenditure in the overweight/obese patient.[7] Early enteral nutrition (EN) and delivery of energy and protein that approximates estimated requirements in the general PICU population have been associated with improved clinical outcomes, including reduced rate of infections, shorter days on mechanical ventilation, and reduced mortality.[8–11] Optimal nutrition practices in the critically ill obese adult patient have been associated with improved clinical outcomes and led to the development of evidence- and consensus-based nutrition guidelines specific for the critically ill obese adult.[12,13] Such practices have included prioritizing measurement of energy expenditure by indirect calorimetry, early initiation of EN, avoiding misconceptions about nutrition reserves, and increased protein delivery (2–2.5 g/kg/d of ideal body weight).[12] Nutrition practices in the pediatric obese population have not been described, yet this cohort of critically ill children is at significant risk for suboptimal nutrition.[14] A description of current nutrition practices in the pediatric obese patient may highlight areas for practice improvement.

In this single-center retrospective cohort study, we aimed to describe nutrition practices for the critically ill overweight/obese child within 3 domains: (1) nutrition screening and assessment, (2) energy and protein prescription, and (3) energy and protein delivery adequacy. We also aimed to compare clinical outcomes, including length of PICU stay, hospital-acquired infections, and mortality, between the overweight/obese study cohort and the general PICU population. We hypothesized that

From the [1]Division of Critical Care Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA; [3]Center for Nutrition, Boston Children's Hospital, Boston, Massachusetts, USA; [4]University of São Paulo–Ribeirao Preto School of Medicine, São Paulo, Brazil; and the [5]Universidad de Chile, Hospital Dr. Luis Calvo Mackenna, Providencia, Chile.

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Corresponding Author:
Enid E. Martinez, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, 300 Longwood, Bader 634, Boston, MA 02115, USA.
Email: enid.martinez@childrens.harvard.edu

critically ill overweight/obese patients would have significantly higher morbidity and mortality compared with the general PICU population and would be characterized by suboptimal nutrition practices.

Materials and Methods

We conducted a single-center retrospective cohort study to describe nutrition practices in overweight and obese children admitted to an academic center PICU between 2010 and 2014. We screened children between the ages of 2 and 21 and with a PICU length of stay >48 hours. We excluded children younger than 2 years as the definition for overweight and obesity status in this age group is not well defined. Children who met the Centers for Disease Control and Prevention (CDC) criteria for overweight (body mass index [BMI] ≥85th percentile and <95th percentile) or obese (BMI ≥95th percentile) nutrition status based on BMI percentile were identified by automated search of the electronic medical records (EMRs).[15–17] The hospital's institutional review board approved this study, and need for consent was waived.

The charts of eligible patient encounters were reviewed and the following data within the predetermined 3 domains were extracted. (1) Nutrition screening and assessment: time to first nutrition assessment by a dietitian and number of follow-up evaluations; initial and follow-up anthropometrics, including weight, height, BMI, and corresponding *z* scores; and skinfold measurements. All patients had been identified to be overweight and obese by BMI percentile recorded in the EMR; we also recorded *International Classification of Diseases, Ninth Revision* (*ICD-9*) billing codes (278.0, overweight and obesity; 278.00, obesity unspecified; 218.01, morbid obesity; 278.02, overweight) to consider clinician recognition of the patients' nutrition status. (2) Energy and protein prescription: initial method of determining energy expenditure (predictive equation or indirect calorimetry [IC]), use of stress factor, and prescribed energy (kcal/kg/d) and protein (g/kg/d). (3) Energy and protein delivery: route of nutrient delivery—oral, EN, or parenteral nutrition (PN); the route of EN (gastric vs postpyloric); time to EN initiation; nil per os (NPO) time; the energy adequacy on days 3 and 7 of PICU admission, defined as the percentage of the estimated energy requirements by the Schofield and World Health Organization (WHO) equations delivered was determined; and protein adequacy on days 3 and 7 of admission, defined as the percentage of the minimum recommended daily age-based protein intake by the American Society for Parenteral and Enteral Nutrition (ASPEN) delivered. We recorded demographic (age, sex), clinical (comorbidities, admission diagnosis, length of PICU stay, need for mechanical ventilation, vasoactive agents), and outcome (mortality and acquired infections 48 hours after admission) variables. We also recorded mortality, length of stay, and hospital-acquired infections in all PICU admissions with stay >48 hours during the study period (2010–2014) to examine for clinical outcome differences between the study cohort and all other concurrent patient encounters.

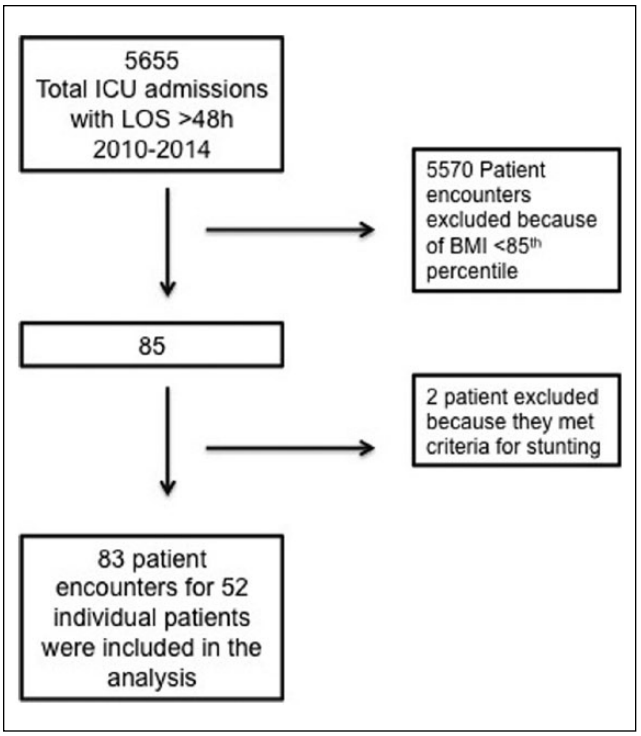

Figure 1. Flowchart of the patient selection process. BMI, body mass index; ICU, intensive care unit; LOS, length of stay.

Length of stay between the study cohort and all other concurrent admissions with PICU stay >48 hours during the study period was compared by the Mann-Whitney test. Rate of hospital-acquired infections and mortality between the 2 groups were compared by the χ^2 test. All data were tested for normality using the D'Agostino and Pearson normality test.[18] Continuous data were presented as median (interquartile range [IQR]); categorical data were presented as frequency (%). Statistical significance was set at $P < .05$.

Results

Data from 83 patient encounters for 52 eligible patients, admitted from 2010–2014, were included in the analyses (Figure 1). Table 1 describes the baseline demographics and anthropometric variables for the cohort. Median (IQR) age was 9.6 (5–15) years, 52% of the cohort was male (27/52), 6% were overweight, and 94% were obese. Comorbidities included neurologic (42.3%), respiratory (28.8%), oncologic (17.3%), and gastrointestinal (GI) disease (15.4%). The most common primary diagnoses on admission were respiratory distress/failure (45.8%), postoperative care (21.7%), and neurologic disease (15.7%). Mechanical ventilation was provided for 64% of the patient encounters for a median duration of 7 days (IQR, 5–25). Vasopressors were required for 24.1% of patient encounters, and median duration of the infusion was 6 days (IQR, 2–10).

Table 1. Baseline Characteristics of Overweight and Obese Children in the Pediatric Intensive Care Unit.[a]

Characteristic	Value
Age, y	9.6 (5–15)
Sex, male	27/52 (52.0)
Comorbidities (n = 52 individual patients)	
Neurological disease	22 (42.3)
Respiratory disease	15 (28.8)
Oncologic disease	9 (17.3)
Gastrointestinal disease	8 (15.4)
Endocrine disease	7 (13.5)
Metabolic/genetic disorders	6 (11.5)
Cardiac disease	2 (3.8)
Renal disease	2 (3.8)
Other	4 (7.7)
Diagnoses on admission (n = 83 patient encounters)	
Respiratory distress/failure	38 (45.8)
Postoperative care	18 (21.7)
Neurological disease	13 (15.7)
Gastrointestinal disease	11 (13.3)
Sepsis/SIRS	9 (10.8)
Postoperative care for T&A	5 (6.0)
Trauma	2 (2.4)
Oncologic disease	2 (2.4)
Post–cardiac arrest care	1 (1.2)
Other	7 (8.4)
Weight, kg	49.5 (24.8–83.4)
WAZ	2.3 (1.8–2.7)
Height, cm	138.7 (107–158)
HAZ	−0.02 (–1.8 to 1.3)
BMI, kg/m^2	27.1 (22.6–33.2)
BMI *z* score	2.3 (1.9–2.7)
BMI percentile	99 (97–99)

BMI, body mass index; HAZ, height for age *z* score; SIRS, systemic inflammatory response syndrome; T&A, tonsillectomy and adenoidectomy; WAZ, weight for age *z* score.
[a]Values are presented as median (interquartile range) or frequency (%).

In comparison to the general PICU admissions during this period, the study cohort had a significantly greater length of PICU stay (8 [5–16] vs 5 [4–9] days, $P < .0001$) and higher PICU mortality rate (6/83 [7.2%] vs 182/5572 [3.3%], $P = .045$). No difference in the rate of hospital-acquired infections was noted between the study cohort and all other concurrent patient encounters during the study period (Table 2).

Nutrition Screening and Assessment

Nutrition screen and a detailed nutrition assessment were recorded during the PICU stay in 50 of 83 (60%) patient encounters and performed within 48 hours of admission for 24% of patient encounters. Follow-up evaluations were completed on average every 3.75 days during the PICU admission. *ICD-9* codes related to overweight or obese status were recorded by the clinical team in 8.4% of patient encounters (7/83).

Energy and Protein Prescription

In most of the 50 patient encounters with recorded nutrition assessment details, standard predictive equations were used to determine estimated energy expenditure. The Schofield equation using actual body weight (Schofield-ABW) was applied in 40% and the World Health Organization (WHO) equation in 18% of these patient encounters.[19,20] The Mifflin–St Jeor was used in 4 patient encounters for energy expenditure estimation in this cohort. A median stress factor of 1.1 (1–1.1) was applied to the estimated energy expenditure in 36 of 50 (72%) patient encounters. A stress factor of >1 was applied to energy expenditure estimates in 44% (20/50). IC was completed for 11 patient encounters (in 9 patients) a median of 9 days from admission. Estimated energy expenditure by both equations was significantly greater than the measured resting energy expenditure values, $P < .0001$, in these 11 patient encounters (Table 3). A daily protein prescription (median value of 1.0 [0.95–1.35] g/kg/d) was recorded in 26 of 50 patient encounters with a completed nutrition assessment.

Energy and Protein Delivery

EN was the only mode of nutrient delivery for 33.7% (28/83) of patient encounters, 25.3% (21/83) gastric and 8.4% (7/83) postpyloric. Median (IQR) time to EN initiation was 2 (IQR, 1–5) days. Median (IQR) duration of NPO status during the PICU course was 4 (IQR, 1–6) days; median time NPO was 33.7% (0–100) of the total PICU stay. PN was a supplemental or exclusive mode of nutrition for 21.7% (18/83) of patient encounters. Median energy delivery adequacy from EN and/or PN was 34.6% (0%–85.6%) and 34.7% (0%–81.1%) on day 3 of PICU admission based on estimated energy expenditure by the Schofield and WHO equations, respectively, and 67.8% (38.1%–94.3%) and 64.4% (37.2%–83.7%) on day 7 of PICU admission. Median (IQR) protein delivery adequacy based on ASPEN age-based recommendations was 22.1% (0%–62.6%) on day 3 of admission and 48.6% (24%–87.2%) on day 7 of admission.

Discussion

We have reported nutrition practices and outcomes in children with BMI ≥85th percentile admitted for >48 hours to a PICU in an academic institution. Obesity or overweight status was not adequately documented in the medical provider billing for the majority of this cohort. The length of stay and mortality rate in the study cohort were significantly greater compared with concurrent PICU admissions. Standard equations for estimating energy requirements with an added stress factor >1.0 were frequently used to determine energy prescriptions for this cohort. IC was completed in a minority of

Table 2. Comparison Between the Overweight or Obese Study Cohort and Concurrent General Pediatric Intensive Care Unit (PICU) Patient Encounters.[a]

Clinical Outcome	Overweight and Obese Study Cohort (n = 83 Patient Encounters)	All Other Concurrent PICU Admissions Cohort (n = 5572 Patient Encounters)	*P* Value[b]	RR (95% CI)
Length of stay	8 (5–16)	5 (4–9)	<.0001	NA
Hospital-acquired infection	2/83 (2.4)	68/5572 (1.2)	.34	1.95 (0.48–7.8)
PICU mortality	6/83 (7.2)	182/5572 (3.3)	.045	3.55 (1.65–7.64)

NA, not applicable; RR, relative risk.
[a]Values are presented as median (interquartile range) or frequency (%). Patients with length of intensive care unit stay >48 hours were eligible.
[b]Length of stay was compared between groups by the nonparametric Mann-Whitney test. Rate of hospital-acquired infection and mortality in the PICU between groups were analyzed by the χ^2 test. Statistical significance was set at $P < .05$.

Table 3. Energy and Protein Prescriptions in Overweight and Obese Children in the Pediatric Intensive Care Unit.[a]

Energy and Protein Prescription	Value
Predictive equations used to estimate energy delivery goal (n = 50 patient encounters)	
Schofield-ABW	20/50 (40)
WHO	9/50 (18)
Home recipe[b]	5/50 (10)
HBE	3/50 (6)
Schofield adjBW	2/50 (4)
Other	11/50 (22)
Frequency of stress factor applied	36/50 (72)
Stress factor applied to predicted EE	1.1 (1–1.1)
Prescribed energy kcal/kg/d (n = 50)	31.1 (24–46.3)
Prescribed protein goal g/kg/d (n = 26)	1 (0.95–1.35)
Indirect calorimetry data (n = 11 patient encounters)	
REE, kcal/kg/d	17 (11.7–24)
Schofield estimated EE, kcal/kg/d	31.2 (23.4–44.5)
WHO estimated EE, kcal/kg/d	36 (23.7–48.1)
RQ	0.89 (0.78–0.91)
VO_2, mL/kg/min	2.4 (1.6–3.4)
VCO_2, mL/kg/min	2.2 (1.4–3)

ABW, actual body weight; adjBW, adjusted body weight; EE, energy expenditure; HBE, Harris-Benedict equation; REE, resting energy expenditure; RQ, respiratory quotient; VO_2, volumetric oxygen consumption; VCO_2, volumetric carbon dioxide elimination; WHO, World Health Organization.
[a]Values are presented as median (interquartile range) or frequency (%).
[b]The baseline prescription for patients on long-term home enteral nutrition via gastrostomy or jejunostomy.

the cohort, where it revealed the inaccuracy of the estimating equations. Protein prescriptions were frequently below the recommended ranges, and the adequacy of protein delivery was suboptimal during the first week in the PICU. Our observations highlight areas for improvement in the nutrition management of overweight and obese critically ill children and future areas for research.

The relationship between overweight/obesity and outcomes in the PICU population is unclear. Increased length of stay and mortality rate have been previously reported in overweight and obese critically ill children, particularly in populations with burn injuries, asthma, and in-hospital cardiac arrest.[2–5] A large retrospective study reported no significant association between obesity and clinical outcomes in the general PICU population.[1] Recently, a large prospective study of mechanically ventilated children reported an association between BMI *z* score >2 and increased prevalence of hospital-acquired infection and lower likelihood of discharge.[6] Obesity has been described as an inflammatory state resulting in a potential for a weakened immune response to critical illness.[21–23] In addition, the metabolic response of a critically ill patient is dominated by protein breakdown and may lead to significant loss of lean body mass in obese patients.[24] Adult studies of obese critically ill patients have demonstrated that early EN and optimal protein intake may improve outcomes.[13] In our current study cohort, we have reported suboptimal energy and protein delivery in the first week of PICU admission.

A timely nutrition assessment for the critically ill patient is recommended by adult and pediatric guidelines.[7,13] Early nutrition assessments allow for identification of the overweight and obese patient and can help development of an optimal nutrition plan. A recent international, multicenter study reporting on clinical outcomes in critically ill children based on nutrition status by BMI *z* score emphasized the importance of identifying not only undernourished but also overweight and obese critically ill children.[6] However, providers are not confident in completing nutrition assessments.[25] The use of nutrition support teams and algorithms that include early nutrition assessments and education regarding nutrition assessments have been shown to improve nutrition practices.[25–28] A nutrition evaluation should include a measure of body composition, as has been recommended by ASPEN's new definition for malnutrition, given the great risk for loss of lean body mass and association with worse clinical outcomes and severe disease in obesity.[7,24,29,30] Measurement of energy expenditure via IC should be prioritized given the risk for inaccurate estimates of energy expenditure, as recommended by ASPEN.[7,31] The risk of overfeeding particularly in chronic intensive care unit patients should be avoided by early and frequent IC measurements of energy expenditure, where available.[32,33] In our current study, nutrition evaluation was recorded in two-thirds of the cohort during the PICU course, but these did not include

body composition measurements, and IC was completed in a minority of the cohort. Early and routine thorough nutrition assessments are desirable for the overweight/obese population and are likely to promote optimal nutrient delivery.

In this study, energy and protein delivery was suboptimal. Patients were NPO for approximately one-third of the PICU stay. Median EN and/or PN energy delivery was less than two-thirds of the estimated requirement, and protein prescription and daily protein intake was below the minimum recommended daily goal of 1.5 g/kg/d for the first week of admission.[7] Protein intake has been associated with improved clinical outcomes. In a recent prospective cohort study of 1245 mechanically ventilated children from 59 international PICUs, greater protein intake adequacy was associated with lower mortality, independent of energy intake.[9] Pediatric critical care nutrition guidelines recommend a minimum of 1.5 g/kg/d of protein intake and up to 3 g/kg/d for children younger than 2 years.[7] Adult nutrition guidelines recommend higher protein delivery goals for the critically ill obese adult patient compared with the nonoverweight/obese patient.[13] Based on our observations, optimizing protein prescription and ensuring the actual delivery of the prescribed protein are areas for practice improvement in critically ill obese and overweight children. The retrospective design of our study did not allow for an evaluation of potential causes for poor energy and protein delivery in this cohort. Adult studies, however, have reported on misconceptions regarding nutrition reserves in the obese/overweight patient population, which may lead to unnecessary delays in nutrition initiation and delivery.[34] In addition, in our study, the postpyloric route was used in only 8.4% of patients, whereas recent multicenter studies have reported use of the postpyloric route in up to 36% of patients receiving EN.[9] Greater difficulties with bedside postpyloric tube placement in this cohort may be possible. Perceived nutrition intolerance is a common reported cause for delayed nutrient initiation and advancement, and assessing for nutrition intolerance in the overweight and obese cohort may be challenging.[14,35,36] Nutrition algorithms have been shown to improve time to EN initiation, reduce unintended fasting times, promote EN advancement, and reduce nutrition intolerance.[26,37] However, nutrition algorithms for the general PICU population may not address specific limitations in nutrient delivery for the overweight/obese PICU patient. Potential cohort specific considerations that may influence nutrient delivery could include alternatives to traditional nutrition intolerance assessments, early placement of a postpyloric tube under fluoroscopy, and emphasis on the need for early EN initiation and optimal protein provision. Further research regarding causes for limited energy and protein delivery in this cohort and potential interventions to improve nutrient delivery is needed.

Our study was limited by its retrospective design and small sample size. We determined overweight and obese status by BMI percentile based on ASPEN's guidelines for the obese hospitalized child, based on prior studies and the American Academy of Pediatrics and CDC recommendations.[15–17] However, we recognize that the best definition for overweight/obese status, particularly in critically ill children, remains unclear. Most studies examining nutrition status in critically ill children have used BMI percentile as the definition for overweight/obese status, but BMI *z* score, weight-for-age *z* score, and weight-for-length *z* score have also been reported.[2–6,38] These definitions are not interchangeable, and different proportions of patients would be considered overweight/obese based on these varied definitions. This may result in failure to capture all overweight/obese patients who were admitted to the PICU in the determined period. Determining overweight/obesity by any of these measures is also influenced by limitations in anthropometric measurements in the PICU. A recent study identified only one-third of PICU patients to have anthropometric measurements on admission.[25] In addition, when anthropometric measurements are obtained, fluid shifts and limitations in patient movement and positioning can also result in inaccurate measurements. Most important, none of these definitions of overweight/obesity status are a measure of fat mass and therefore are not a substitute for body composition assessments.[38,39] These limitations reinforce the importance of comprehensive nutrition evaluations in this cohort, including, when available, IC to measure energy requirements and an assessment of body composition. Further research to investigate the correct proxy measure for fat mass in children should be considered. A uniform definition for overweight/obesity status in critically ill children is desirable for clinical and research purposes.

Conclusion

Overweight and obese children had suboptimal assessments and nutrient delivery during their PICU course. Mortality and duration of PICU stay were greater compared with the general PICU population. Nutrition assessment; optimal energy prescriptions, guided by IC where available; and optimal delivery of energy and protein must be emphasized. The impact of these practices on clinical outcomes must be investigated.

Statement of Authorship

E. E. Martinez, K. A. Ariagno, E. Muñoz, and N. M. Mehta contributed to the conception/design of the research; E. E. Martinez, K. A. Ariagno, N. Stenquist, D. Anderson, and N. M. Mehta contributed to the acquisition, analysis, or interpretation of the data; and E. E. Martinez and N. M. Mehta drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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From Evidence to Clinical Practice: Positive Effect of Implementing a Protein-Enriched Hospital Menu in Conjunction With Individualized Dietary Counseling

Tina Munk, PhD[1]; Nina Bruun, RD[2]; Michael A. Nielsen, Pb[3]; and Thordis Thomsen, PhD[4]

Abstract

Background: The aim of this study was to investigate if a protein-enriched menu in conjunction with individualized dietary counseling would increase energy and protein intake in hospitalized patients at nutrition risk compared with providing the protein-enriched menu as a stand-alone intervention. *Method:* Data from medical and surgical hospitalized patients were prospectively collected and compared with a historical intervention group (HIG). Primary outcome was the number of patients achieving >75% of energy and protein requirements. Secondary outcomes included mean energy and protein intake (adjusted for body weight [ABW]), readmission rate, and the number of patients with a baseline intake <50% of energy and protein requirement, who increased to ≥50%. *Results:* In the intervention group (IG), 92% vs 76% in the HIG reached >75% of energy requirements (P = .04); 90% in the IG vs 66% in the HIG reached >75% of protein requirements (p = <0.01). The IG had a significantly higher mean intake of energy and protein compared with the HIG: ABW, 31 kcal kg^{-1} vs 25 kcal kg^{-1} (P < .01) and 1.2 g protein kg^{-1} vs 0.9 g protein kg^{-1} (P < .001). More than 85% of the patients with a baseline <50% of the EP requirement achieved ≥75% of the energy and protein requirement. No difference between readmission rates was found. *Conclusion:* Providing a protein-enriched menu in conjunction with individualized dietary counseling significantly increased protein and energy intake in hospitalized patients at nutrition risk. (*Nutr Clin Pract*. 2017;32:420-426)

Keywords

hospital food service; menu planning; nutritional status; malnutrition; dietary proteins

The prevalence of patients at nutrition risk in European hospitals is reported to be around 30%.[1] A large proportion of these patients are at nutrition risk on admission,[1–3] and due to inadequate intake of nutrition requirements, most experience further deterioration in nutrition status during hospitalization.[1,3,4] Being at nutrition risk is associated with a wide range of adverse effects (eg, increased morbidity, prolonged hospital stays, increased healthcare costs, poorer quality of life [QoL], increased readmission rates, and higher mortality rates).[1,5–9]

Food is endorsed as the first choice for treating undernutrition. Compared with tube feeding or parenteral nutrition (PN), oral food intake is associated with a lower risk of complications and side effects (eg, infection, aspiration, overfeeding, and more affordable cost). Furthermore, the use of food as nutrition treatment is an attractive choice since food is able to address the sociocultural and hedonic aspects of food, such as sensory pleasure, and social and cultural habits associated with eating, as opposed to oral nutrition supplements, tube feeding, and PN. Furthermore, an oral diet is applicable in approximately 75% of hospitalized patients,[10] making hospital food a very important strategy in the treatment of undernutrition in the hospital setting. However, quality research regarding the effect of hospital food on nutrition intake for nutritionally at-risk hospitalized patients is limited.

In a randomized controlled trial (RCT), we recently demonstrated a significant positive effect on energy and protein intake in nutritionally at-risk hospitalized patients using a protein-enriched hospital menu.[11] The intervention doubled the number of patients achieving ≥75% of their energy and protein requirements (66% in the intervention group vs 30% in the control group reached ≥75% of their energy and protein requirements; P = .001).[11]

Due to the positive effect, financial resources were allocated to implement the protein-enriched hospital menu in selected departments at Herlev University Hospital (HUH). We

From the [1]Nutritional Research Unit, Herlev Gentofte University Hospital, Herlev, Denmark; [2]Municipality of Ballerup, Ballerup, Denmark; [3]Nutritional Research Unit, The Nordic Kitchen, Herlev Gentofte University Hospital, Herlev, Denmark; and the [4]Abdominal Centre, Rigshospital, Copenhagen University Hospital, Copenhagen, Denmark.

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Corresponding Author:
Tina Munk, PhD, Nutritional Research Unit, Herlev Gentofte University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark.
Email: tina.munk@regionh.dk

further decided to provide the protein-enriched hospital menu in conjunction with individualized dietary counseling by registered clinical dietitians (RDs) as prior studies have shown a positive effect of dietary counseling by RDs on energy and protein intake, body weight, QoL, and readmissions.[10,12,13]

The present study therefore aimed to determine whether provision of the previously tested protein-enriched hospital menu in conjunction with individualized dietary counseling would demonstrate a greater effect on energy and protein intake in hospitalized patients at nutrition risk compared with providing the protein-enriched hospital menu as stand-alone intervention.

Materials and Methods

Study Design and Participants

Study participants were recruited from January to August 2014. Study participants were, as in the RCT,[11] recruited from the medical and surgical departments at HUH.

Inclusion and exclusion criteria were the same as in the previously published RCT[11]:

> Inclusion criteria: Newly admitted patients aged >18 years who were at nutrition risk according to the validated nutrition risk screening tool (NRS-2002, ≥3),[14] had an oral intake <75% of requirement, were able to eat orally, and had an anticipated length of hospital stay (LOS) ≥3 days
> Exclusion criteria: Dysphagia, food allergy or intolerance, anatomical obstructions preventing oral food intake, patients who were supplemented partly or totally with enteral nutrition (EN) or PN, and terminally ill patients

Enrollment of the Patients

Nursing staff referred potentially eligible patients to the dietetic unit. Nursing staff were to collect baseline nutrition data on energy and protein intake by performing a "1-day dietary record" of the patients' nutrition intake. If the patient was at nutrition risk and had an estimated nutrition intake <75% of the requirement according to the 1-day dietary record, they were to refer the patient to the dietetic unit.

In the dietetic unit, 3 RDs were dedicated to the project. They rescreened patients for eligibility to make sure that they met the inclusion criteria.

The Intervention

The patients of the intervention group (IG) received the protein-enriched hospital menu consisting of an a la carte menu of small dishes rich in energy-dense ingredients and enriched with a high-quality protein powder (milk-based protein powder). The menu consisted, for example, of different kinds of desserts (crunchy apple cake, buttermilk dessert, etc), soups, meat, and fish dishes (Table 1). It was the same menu as used in the previously published RCT.[11]

Furthermore, the IG was given individualized dietary counseling by an RD. The individualized dietary counseling included estimation of the patient's nutrition requirements and a diet intake assessment to estimate percentage of nutrition coverage. Also, we surveyed the dietary history of the patient using a 24-hour recall method. The survey included a face-to-face interview to determine the patient's usual meal pattern and sociocultural and sensory desires with regard to food. The aim was to tailor a nutrition plan to the patient's preferences for different kinds of foods items.

On a daily basis, the RDs evaluated the patients' nutrition intake with regard to nutrition requirements. If necessary, the RDs encouraged and provided nutrition guidance to patients or the nursing staff to support patients' chances of obtaining an adequate nutrition intake.

Furthermore, the role of the RDs was also to take the patients' food orders. This allowed the RDs to encourage patients to include a glass of milk with their food. Patients could order dishes by telephone, and the dishes were served within 30 minutes by RDs using a "room service" approach (ie, the food was presented, before it was served). If required, ward staff or RDs assisted patients in ordering the food.

A special trolley was developed to store and keep the dishes cold at the departments until serving. The dishes were designed so they were easy to eat with only a fork or spoon, and all the hot dishes were designed to be heated in a microwave. The menu supplemented the standard hospital food service for nutritionally at-risk patients. Patients could order as many dishes as they liked between 11:15 AM and 6:15 PM Monday to Sunday. If the patients wanted a late-night dish, the RDs put the dish aside for the evening/night with the patient's name on it. These dishes were later served by the nursing staff. On the weekends, the food was served by kitchen staff. Consequently, no dietetic counseling was provided on the weekends. Nursing staff was responsible for preparing patients for eating and for assisting patients who were unable to eat by themselves. Figure 1 summarizes the intervention.

Standard Hospital Food Service for Nutritionally At-Risk Patients

The standard hospital food service offers 3 main meals (breakfast, lunch, dinner) and 2–3 in-between meals served from a buffet. The national nutrition guidelines for this diet, with energy and protein-rich beverage (ie, milk) included, recommend that the standard hospital diet on average contains 2143 kcal, 95 g of protein (15–20 E%), 100 g of fat (40–50 E%), and 225 g of carbohydrate (40–45 E%) per day.[15]

Protein-Enriched Hospital Menu vs the Standard Diet for Patients at Nutrition Risk

The protein-enriched hospital menu was designed to fulfill, as a minimum, the same criteria for energy and protein

Table 1. The Protein-Enriched Hospital Menu.[a]

Menu	Portion Size, g	Energy, kcal	Protein, g
Breakfast dishes			
Omelet with bacon	60	167	9.1
Breakfast muffin with butter, cheese, and jam	100	361	11.5
Rye bread porridge with fresh vanilla cream	90	88	7.4
Soups			
Clear soup with vegetables, meatballs, and dumplings	79	23	6.9
Classic mushroom soup	75	111	8.2
Fish dishes			
Baked salmon with egg coleslaw, hazelnuts, and olive tapenade	70	182	8.9
Slightly smoked trout seasoned with egg salad and fresh chervil	55	129	8.0
Meat dishes			
Meatloaf with game sauce and cranberries	73	107	7.6
Meatballs of veal with stewed cabbage and béchamel sauce	55	112	6.5
Crispy fried fish crépine with Jerusalem artichokes in cream sauce	75	171	7.5
Chicken sticks with peanut butter	55	176	7.9
Side dishes			
Mashed sweet potatoes with onion and bacon	68	157	6.4
Torta di risotto with fried mushrooms, herbs, and lemon peel	47	98	7.7
Warm potato omelet with a compote of pickled red onions	50	128	6.1
Baked cauliflower cream with roasted nuts and pickled cucumbers	60	93	7.1
Mashed root vegetables with browned butter	75	150	6.1
Desserts			
Chocolate confection of marzipan and nougat	52	245	6.3
Crunchy apple cake with peel of orange	90	194	7.3
Compote of berry with vanilla cream	95	143	6.0
Mild fromage with cream and chocolate	68	148	7.6
Buttermilk dessert with lemon and small cookies	100	199	6.9
Hot chocolate with whipped cream	110	191	6.2
Parfait with strawberry	80	219	7.0

[a]Reflects portion size, energy, and protein content of all the 23 dishes of the novel menu.

content as the standard food menu described above. To reach one's daily nutrition requirements solely from the novel menu, patients needed to consume 2 dishes of the novel menu 6 times daily and drink 2 glasses of whole milk. This would, on average, provide patients with 2071 kcal and 102 g of protein.

Outcomes

The primary outcome was the percentage of patients reaching ≥75% of their protein and energy requirements as a mean intake over 3 days. This nutrition target was based on a previous trial reporting that weight stability can be achieved with this level of intake.[16] Secondary outcomes were mean energy and protein intake (adjusted for body weight [ABW]) and readmission rate, which were defined as readmission within 30 days after discharge. These data were compared with the historical intervention group (HIG) data.

In the IG, we also investigated the number of patients with a baseline intake <50% of the energy and protein requirement, who increased to ≥50%. We included this outcome as some studies have found an increased risk of death at an intake <50% of requirements.[8,17] Furthermore, we investigated meal patterns with regard to protein intake in the IG. These data were of interest since it is suggested that the best way to stimulate protein synthesis is by ingestion of 90 g of protein evenly distributed over 3 meals.[18–20]

Energy and Protein Intake

Energy and protein were calculated consecutively as a mean intake over 3 days. As in the HIG, a detailed nutrition registration form was used to distinguish between different meal components. The amounts consumed of each portion of food/beverage were visually assessed and recorded in quartiles (0%, 25%, 50%, 75%, and 100%) by the nursing staff, the patients, or the RDs. This is a validated method to assess food intake.[21] Both in the HIG and in IG, the RDs collected records daily and conducted short daily dietary recall interviews to verify the content of patients' dietary records.

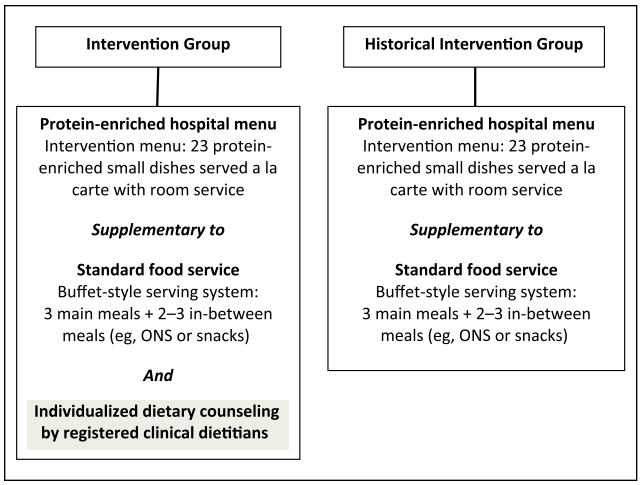

Figure 1. Summary of the intervention. ONS, oral nutrition supplement.

Estimation of Energy and Protein Requirements

Patients' energy requirements were estimated according to Danish guidelines for hospitalized patients: the basal metabolic rate (BMR) multiplied by an estimated activity factor (× 1.1 if bedridden and × 1.3 if able to walk around on the ward) and by a stress factor in case of fever (× 1.2 [38°C], 1.3 [39°C], 1.4 [40°C]) or, if body mass index (BMI) <18.5 kg/m^2, a factor for weight gain (× 1.3).[14] The BMR was calculated by the Harris-Benedict equation (men: BMR = 66.5 + 13.8 Weight + 5.0 Height – 6.8 Age; women: BMR = 655+ 9.6 Weight + 1.8 Height – 4.7 Age). Protein requirements were set at 18 E% of the energy requirement as recommended in Danish institutional diet guidelines.[14]

Statistics

Statistical analyses were carried out using SPSS version 18.0 (SPSS, Inc, an IBM Company, Chicago, IL). Descriptive statistics were used to calculate means and standard deviations (SDs). We used Pearson's χ^2 test to test differences between categorical data. Independent *t* tests were used for interval scale variables. Mean energy and protein intake according to body weight (BW) was calculated.

For categorical outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) and, for significant results, numbers needed to treat (NNTs); for continuous outcomes, we calculated mean differences (MDs) with 95% CIs.

Ethical Aspects

The project was approved by the Danish Data Protection Agency (ID: HEH-2014-045). The Danish Regional Committee on Biomedical Research was contacted in regard to the need for their approval. As the study was considered a quality project, the committee deemed there was no need for a formal approval.

Results

Study Population

Overall, data from 50 intervention patients and 41 historical intervention patients were included (Table 2). Patient characteristics are presented in Table 2. At baseline, the IG and HIG patients were similar with respect to age, sex, weight, and nutrition risk. Both groups consisted of medical (primary diagnosis: chronic obstructive lung disease, nonsurgical cancer, infectious diseases such as pneumonia and urinary tract infections) and surgical patients (primary diagnosis: cancer and femoral neck fracture).

Outcome

Primary outcome. Significantly more IG patients compared with HIG patients achieved an intake of ≥75% of their energy (IG: 92%, HIG: 76%; $P = .04$) and protein requirements (IG: 90%, HIG: 66%; $P < .01$) (Table 3). The RR for reaching ≥75% of their energy and protein requirement was 1.37 (95% CI, 1.08–1.74), and NNT was 4.

Secondary outcomes. The IG had a significantly higher mean energy intake compared with the HIG (MD, 230 kcal; $P = .001$) (Table 3). When calculating energy intake according to ABW, we also found a significantly higher mean intake in the IG group (MD, 7 kcal kg^{-1}; $P < .001$) (Table 3).

Mean protein intake was also significantly higher (MD, 11 g kg^{-1}; $P < .001$) in the IG. According to ABW, the IG reached 1.2 g kg^{-1} whereas HIG had a mean intake of 0.9 g kg^{-1} (MD, 0.3 g kg^{-1}; $P < .001$) (Table 3).

Nutrition baseline data were available in 17 of 50 patients in the IG. At baseline, 14 of 17 had an intake <50% of energy requirement. Of these, 12 of 14 achieved ≥75% of energy requirement at follow-up. At baseline, 17 of 17 had an intake <50% of protein requirement. Of these, 16 of 17 achieved ≥75% of protein requirement at follow-up. Comparison to the HIG was not possible since these data were not collected in the RCT.[11]

Meal patterns with regard to protein showed the following distribution across meals: an average 14 g at breakfast, 18 g at lunch and dinner, and 4 g in the 3 in-between meals. Readmission rates did not differ between groups (IG: 16; HIG: 14).

Discussion

Primary Outcome

The protein-enriched hospital menu in conjunction with individualized dietary counseling significantly increased the number of patients achieving ≥75% of their protein and energy intake in hospitalized patients at nutrition risk compared with providing the protein-enriched hospital menu without dietary counseling. Indeed, 90% (45/50) reached ≥75% of their protein and energy requirement. This equals an increase of 24%

Table 2. Characteristics of Hospitalized Patients Enrolled in the Study.

Characteristic	IG	HIG	*P* Value
No. of patients	50	41	
Sex, No.			.5
Male	16	16	
Female	34	25	
Age, mean ± SD, y	74 ± 14	75 ± 10	.7
Weight, mean ± SD, kg	19 ± 3	21 ± 4	.08
Nutrition risk assessment, No.			
Score = 3	23	17	
Score = 4	22	14	
Score = 5	4	7	
Score = 6	1	3	
Total, mean ± SD	3.7 ± 0.7	3.9 ± 0.9	.2

HIG, historical intervention group; IG, intervention group.

Table 3. Results of Primary and Secondary Outcomes.

Characteristic	IG (n = 50)	HIG (n = 41)	Risk Ratio (95% CI)	Mean Difference, IG/HIG (95% CI)	*P* Value
Primary outcome					
Coverage of ≥75% of nutrition requirements, No. (%)					
Energy	46 (92)	31 (76)			.04[a]
Protein	45 (90)	27 (66)			<.01[a]
Energy and protein	45 (90)	27 (66)	1.4 (1.08–1.74)		<.01[a]
Secondary outcome					
Mean (SD) intake					
Energy, kcal kg^{-1}	1618 (483)	1391 (395)		230 (33–427)	.001[b]
Protein, g kg^{-1}	63 (17)	53 (16)		11 (3.5–18.3)	<.001[b]
Mean (SD) intake according to body weight					
Energy, kcal kg^{-1}	31 (12)	25 (9)		7 (3–11)	<.001[b]
Protein, g kg^{-1}	1.2 (0.4)	0.9 (0.4)		0.3 (0.2–0.5)	<.001[b]

HIG, historical intervention group; IG, intervention group.
[a]Pearson's χ^2 test.
[b]t test.

(from 66% to 90%) by including dietary counseling by RDs in the intervention. Individualized dietary counseling by RDs in combination with a delicious protein-rich menu must therefore be recognized as a very effective strategy for improving the nutrition status of hospitalized patients at nutrition risk. Furthermore, offering dietary counseling may also allow for change in the patients' dietary habits that may persist beyond discharge and thus result in maintenance of any nutrition-related benefits achieved in the hospital.[22]

Secondary Outcome

The mean intake of energy (31 kcal kg^{-1}) and protein (1.2 g kg^{-1}) supports the effectiveness of including RDs. Patients had an energy intake equivalent to BMR multiplied by 1.3, which at least would keep them weight stable. In the HIG, the mean energy intake was 25 kcal kg^{-1}, indicating that only the BMR was covered. Furthermore, the amount of protein consumed in the IG follows the general recommendation for protein requirements during illness.[23,24]

The study further showed a positive effect on the patients who achieved below 50% of energy and protein requirements at baseline. At follow-up, the patients had increased energy and protein intake to ≥75% of requirements, indicating that the intervention may potentially also affect survival positively.[8,16] However, due to lack of clinical data and the use of a surrogate primary outcome measure, no firm conclusions can be drawn in this regard.

Readmission rate did not differ between groups. Generally, hospital stays are getting shorter, leaving limited time to

improve nutrition status. One explanation for the similar readmission rates may therefore be insufficient nutrition follow-up after discharge. In fact, a recent study showed a clear tendency in decreasing hospital readmissions when dietetic counseling by RDs was provided in the patients' home after discharge.[12]

It has been reported that even short hospital stays may lead to loss of functional capacity and the ability to cope with activities of daily living (ADLs).[25] Therefore, it is of great importance to investigate how to stimulate muscle anabolism during the hospital stay.

Some studies suggest that a high (90 g of protein) protein ingestion evenly distributed at 3 daily meals (30 g per meal) has a better stimulating effect on protein synthesis and thereby muscle anabolism compared with an uneven distribution.[17,18] The IG data showed more or less an even distribution of protein (breakfast: 14 g; lunch and dinner: 18 g), but ingestion did not reach 25–30 g of protein as recommended.[17–19] Especially the protein ingestion at breakfast was low, which may be unfortunate after a long-night fast. However, the evidence regarding the effect of protein meal patterns is still too sparse to draw any firm conclusions. In a future RCT, it would be relevant to investigate the effect of increasing protein intake in the 3 main meals on protein synthesis.

Strength and Limitations of the Study

Due to the design of this intervention study, obvious methodological limitations must be taken into consideration. The use of a historical control group increases the risk of selection bias, and lack of blinding of the intervention increases risk of performance and detection bias. However, due to similarity of the baseline characteristics, the risk of potentially important factors influencing the results of this study is considered moderate. However, it is important to recognize that a central strength of this study is that the menu has been thoroughly tested in a previous RCT.[11] We just included individualized dietary counseling as part of the intervention, in an attempt to increase the number of patients receiving sufficient energy and protein. Furthermore, the external validity of this study is considered relatively high since it has been tested in both medical and surgical patients at nutrition risk.

Implications for Practice

The protein-enriched hospital menu has now been extensively tested in the clinical practice. The menu can fairly easily be implemented in other Danish hospitals to ethnic Danish patients at nutrition risk since the recipes are not classified. In other countries and cultures, the overall concept can also be implemented. However, identification of cultural differences (ie, taste differences in the target population) is necessary for deciding which dishes to include in the menu.

Another issue to consider is the cost of the concept, including both the protein-enriched hospital menu and dietary counseling. The concept has not been economically evaluated. An unpublished cost analysis estimated that the cost of 1 dish is on average 0.3 EUR/USD, which equals 4 EUR/4.3 USD a day if a patient's energy and protein requirements are to be covered by the menu. Furthermore, the cost of implementing the whole concept in 150 nutritionally at-risk patients, including food production and RDs, is estimated to reach around 350.000 EUR/376.000 USD annually. This may be considered a relatively high cost. However, given the major economic consequences of undernutrition, individually and for society,[26] translation of the concept may potentially constitute a relatively low-cost intervention for addressing undernutrition in hospitalized patients.

However, to lower the cost of the concept, one could consider bringing in lower-paid staff instead of RDs to take care of the food orders and food delivery in favor of using the RDs for dietary counseling and daily follow-up. However, we have experienced a very positive effect of RDs handling the whole part of the concept. The RDs very quickly established a positive professional relationship with the patient, probably due to multiple "visits" during the day. Perhaps it may also be related to the satisfaction of getting appetizing and delicious menus. In the experience of the RDs, this positive professional relationship was advantageous for helping/convincing/tempting patients to increase their nutrition intake. For example, it enabled them to suggest, while on the phone with patients, to drink a glass of milk with their food or to tempt them with an extra dessert or to order a dish for a late-night snack.

Conclusion

A special nutrition concept including a thoroughly tested protein-enriched hospital menu in conjunction with individualized dietary counseling by RDs had a significant positive impact on energy and protein intake in hospitalized patients at nutrition risk. Because 90% of the included patients reached at least 75% of their energy and protein intake, we consider this special concept, including both a protein-enriched hospital menu and dietary counseling, an effective strategy to combat undernutrition in the hospital setting.

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Statement of Authorship

T. Munk, N. Bruun, and M. A. Nielsen contributed to the design of research; T. Munk and N. Bruun contributed the acquisition and analysis of data; T. Munk, N. Bruun, and T. Thomsen

contributed to the interpretation of the data; and T. Munk and T. Thomsen drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved the final manuscript.

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Parenteral Nutrition Lipid Injectable Emulsion Products Shortage Considerations

Steve Plogsted, PharmD, BCNSP, CNSC[1]; Stephen C. Adams, MS, RPh, BCNSP[2]; Karen Allen, MD[3]; M. Petrea Cober, PharmD, BCNSP, BCPPS[4]; June Greaves, RD, CNSC, CD-N, LD, LDN[5]; Amy Ralph, MS, RD, CNSC, CSO, CDN[6]; Daniel T. Robinson, MD[7]; Kim Sabino, MS, RD, CNSC[8]; Renee Walker, MS, RD, LD, CNSC, FAND[9]; Ceressa T. Ward, PharmD, BCPS, BCNSP, BCCCP[10]; Joe Ybarra, PharmD, BCNSP[11]; and Beverly Holcombe, PharmD, BCNSP, FASHP, FASPEN[12]; Nutrition Product Shortage Subcommittee, Clinical Practice Committee, American Society for Parenteral and Enteral Nutrition

Keywords
lipids; lipid injectable emulsion; drug shortages; intravenous fat emulsions; intravenous lipid emulsion; nutritional support; parenteral nutrition; essential fatty acids

The American Society for Parenteral and Enteral Nutrition (ASPEN) is a professional society of physicians, nurses, dietitians, pharmacists, other allied health professionals, and researchers. ASPEN envisions an environment in which every patient receives safe, efficacious, and high-quality patient care. ASPEN's mission is to improve patient care by advancing the science and practice of clinical nutrition and metabolism. ASPEN has developed parenteral nutrition (PN) shortage considerations to assist its members and other clinicians in coping with PN shortages for their patients.

These lipid injectable emulsion (ILE) (also known as intravenous fat emulsion) product shortage considerations were approved by the ASPEN Clinical Practice Committee and the Board of Directors on December 21, 2016.

For the most up-to-date product shortage information, see these websites:

- American Society of Health-System Pharmacists (ASHP), Drug Shortages Resource Center (http://www.ashp.org/shortages)
- U.S. Food and Drug Administration (FDA) drug shortages (http://www.fda.gov/Drugs/DrugSafety/DrugShortages/)
- ASPEN Product Shortage Latest News (https://www.nutritioncare.org/public-policy/product-shortages/)

During an ILE products shortage period, consider 1 or more of the following measures:

1. Assess and routinely reassess each patient as to the indication for PN and provide nutrition via the oral or enteral route when possible.
2. Purchase only as much ILE supply as needed. In the interest of fair allocation to all patients nationally, please do not stockpile.
3. During prolonged shortages of ILE products, the U.S. FDA may approve the temporary importation of alternative products. These products may have different oil emulsion components, fatty acid sources and amounts, and packaging and labeling compared with products available in the U.S. The Dear Healthcare Professional Letter accompanying imported products should be carefully reviewed before implementing clinical use. Members of the healthcare team should be educated on any differences between imported ILE products and ILE products approved for use in the U.S.
4. Compound PN in a single, central location (either in a centralized pharmacy or as outsourced preparation) to decrease inventory waste. Consider a supply outreach to other facilities in your geographic location.

From the [1]Nationwide Children's Hospital, Columbus, Ohio, USA; [2]VITALine Infusion Pharmacy Services, Geisinger Medical Center, Danville, Pennsylvania, USA; [3]University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA; [4]Akron Children's Hospital, Akron, Ohio, USA; [5]Coram/CVS Specialty Infusion Services, Denver, Colorado, USA; [6]Yale–New Haven Hospital, New Haven, Connecticut, USA; [7]Division of Neonatology, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [8]Saint Francis Hospital and Medical Center, Hartford, Connecticut, USA; [9]Michael E. DeBakey Veteran Affairs Medical Center, Houston, Texas, USA; [10]Emory Healthcare, Atlanta, Georgia, USA; [11]Medical City McKinney, McKinney, Texas, USA; and [12]ASPEN, Silver Spring, Maryland, USA.

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Corresponding Author:
Beverly Holcombe, PharmD, BCNSP, FASHP, FASPEN, ASPEN, 8630 Fenton St, Suite 412, Silver Spring, MD 20910, USA.
Email: beverlyh@nutritioncare.org

5. Facilities and practitioners need to continue to observe and be compliant with the product labeling (eg, package insert), U.S. Pharmacopeia General Chapter <797> Pharmaceutical Compounding—Sterile Preparations, and state boards of pharmacy and federal rules and regulations.
6. Include PN component shortages and outages in the healthcare organization's strategies and procedures for managing medication shortages and outages. These procedures should include a process:
   a. to identify and monitor patients who do not receive ILE,
   b. to notify providers when a shortage situation occurs, and
   c. to notify patients receiving long-term (eg, longer than 1 month) PN therapy and their caregivers when their PN formulation has been adjusted for shortages and outages of PN components.
7. Prioritize supply of soybean oil–based ILE as follows:
   a. Neonatal and pediatric hospitalized patients should continue the same ILE therapy as before the shortage to minimize risk of adverse effects associated with essential fatty acid deficiency (EFAD) in this high-risk patient population. Priority for ILE during critical shortages should be given to neonates followed by pediatric patients and, finally, adolescent patients.
   b. Adult, mild to moderately malnourished hospitalized patients receiving PN less than 2 weeks may have ILE withheld during a shortage unless it is considered essential in the judgment of the healthcare professional.
   c. Adult, hospitalized patients receiving PN longer than 2 weeks should receive a total of 100 g of a soybean oil–based ILE weekly for EFAD prevention,[1] which should be provided by the safest and most efficient method that minimizes waste. The remainder of nonprotein energy may be provided by dextrose unless not indicated clinically, such as hyperglycemia, hypertriglyceridemia, and obesity. ILE should be provided as a component of daily energy based on current practice recommendations prior to the shortage for some specific adult hospitalized patients (eg, patients with glucose intolerance, severely malnourished patients, patients at risk for refeeding syndrome, during pregnancy). Patients should be monitored for EFAD. See item 8 for more information on EFAD.
   d. Adult, hospitalized, critically ill patients receiving propofol should not require additional ILE for EFAD prevention since the soybean oil in the medication will supply needed essential fatty acids (EFAs).
   e. Home or long-term care patients receiving PN should continue to receive the same ILE therapy as before the shortage. However, ILE should be minimized when clinically feasible. At a minimum, patients should receive a total of 100 g of a soybean oil–based ILE weekly for EFAD prevention, which should be provided by the safest and most efficient method that minimizes waste. The remainder of nonprotein energy should be provided by dextrose unless not indicated clinically, such as hyperglycemia, hypertriglyceridemia, and obesity. ILE should be provided as a component of daily energy based on current practice recommendations prior to the shortage for some specific adult home or long-term PN patients (eg, patients with glucose intolerance, severely malnourished patients, patients at risk for refeeding syndrome, during pregnancy). Patients should be monitored for EFAD. See item 8 for information on EFAD.
8. Monitor closely patients receiving PN for developing EFAD when your institution is experiencing ongoing shortages. Increase awareness and assessment for signs and symptoms of EFAD. Signs and symptoms of EFAD include but are not limited to alopecia, thrombocytopenia, anemia, impaired wound healing, and diffuse dry, scaly rash. Biochemical evidence of EFAD is confirmed by a triene-to-tetraene ratio greater than 0.2.[1,2] Using topical oils for the prevention and treatment of EFAD has produced mixed results. Safflower and sunflower seed oils had beneficial results, whereas vegetable oil (corn oil) did not.[3–7]
9. Consider using an alternative ILE product such as a 4-oil product (soybean oil, medium-chain triglycerides, olive oil, and fish oil) during a soybean oil–based ILE shortage. This product is only approved for use in adults in the U.S. The doses and frequency of administration to meet EFAs needs for adults may be different from soybean oil–based ILE. Consult the manufacturer for specific information on meeting EFAs needs. The healthcare team should be educated on the differences between alternative ILE products and soybean oil–based ILE products.
10. In the event of a 4-oil (soybean oil, medium-chain triglycerides, olive oil, and fish oil) ILE shortage, use standard soybean oil–based ILE dosing and frequency to meet patients' EFAs needs.
11. Report severe drug product shortage information to the FDA Drug Shortage Program (DSP) (http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm142398.htm).
12. Report any patient adverse events or medication hazard related to shortages to the Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program (https://www.ismp.org/errorReporting/reportErrortoISMP.aspx).

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Suggested Readings

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Response to "Enteral Formulas in Nutrition Support Practice: Is There a Better Choice for Your Patient?"

In their excellent article entitled "Enteral Formulas in Nutrition Support Practice: Is There a Better Choice for Your Patient?"[1] Escuro and Hummell discuss the possibilities that enteral nutrition formulae with a high content of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) may exacerbate and play a role in the pathogenesis of enteral feeding–related diarrhea.

This conclusion was based on a series of articles published by Professor Gibson and his colleagues from Melbourne.[2,3] At the time of writing their article, Escuro and Hummell[1] would not have been aware that Gibson et al recently reevaluated the analytic technique used to quantitate the FODMAP content of enteral formulas.[4] Importantly, they found that the content had been overestimated due to the high concentrations of maltodextrins in the diet.[4] In contrast to the conclusions initially drawn, it now seems very unlikely that the FODMAP contents of enteral formulae are involved in the pathophysiology of enteral feeding–related diarrhea.[5] Indeed, since FODMAPs are metabolized in the right colon to gas and short chain fatty acids (SCFAs), it is more likely that at the actual concentrations present, they have a beneficial effect, as SCFAs stimulate colonic water and electrolyte absorption.[6] Moreover, it must be remembered that components of FODMAPs (eg, fructooligosaccharides) constitute part of the fiber blends in some enteral formulae. These blends have been shown to actually reduce bowel frequency when baseline frequency was high in enterally fed patients.[7]

D. B. A. Silk, MD, AGAF, FRCP
Imperial College London, London, UK

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