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The Critical Care Obesity Paradox and Implications for Nutrition Support

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Abstract Obesity is a leading cause of preventable death worldwide. The prevalence of obesity has been increasing and is associated with an increased risk for other co-morbidities. In the critical care setting, nearly one third of patients are obese. Obese critically ill patients pose significant physical and on-physical challenges to providers, including optimization of nutrition therapy. Intuitively, obese patients would have worse critical care-related outcome. On the contrary, emerging data suggests that critically ill obese patients have improved outcomes, and this phenomenon has been coined "the obesity paradox." The purposes of this review will be to outline the historical views and pathophysiology of obesity and epidemiology of obesity, describe the challenges associated with obesity in the intensive care unit setting, review critical care outcomes in the obese, define the obesity-critical care paradox, and identify the challenges and role of nutrition support in the critically ill obese patient.

Keywords Obesity · Critical care · Intensive care · Nutrition · Enteral nutrition · Parenteral nutrition · Permissive underfeeding

Abbreviations

ABW	Actual body weight
ASPEN	American Society of Enteral and Parenteral Nutrition
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
EN	Enteral nutrition
ESPEN	European Society of Parenteral and Enteral Nutrition
HR	Hazard ratio
IBW	Ideal body weight
IC	Indirect calorimetry
ICU	Intensive care unit
OR	Odds ratio
PEEP	Positive end-expiratory pressure
PN	Parenteral nutrition
PSU	Penn State University
SAD	Sagittal abdominal diameter
SCCM	Society of Critical Care Medicine

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Introduction

Obesity is the second leading cause of preventable death worldwide. In the USA, obesity prevalence is on the rise and

is associated with an increased risk for additional disease acquisition, such as ischemic heart disease, diabetes, and cancer. One third of critically ill patients are obese [1]. This disease process poses significant challenges to the critical care provider. These inferences suggest that obese critically ill patients could have worse outcomes, as compared to non-obese critically ill patients. Instead, emerging data suggests that critically ill obese patients have improved outcomes, and this phenomenon has been coined "the obesity paradox." Additionally, therapies such as nutrition support for the critically ill obese remain challenging. The purposes of this review will be to outline the historical views and pathophysiology of obesity and epidemiology of obesity, describe the challenges associated with obesity in the intensive care unit setting, review critical care outcomes in the obese, define the obesity-critical care conundrum, and identify the challenges and role of nutrition support in the critically ill obese patient.

Historical Views of Obesity

Today, the public's perception of obesity is attributed to poor lifestyle choices associated with a lack of willpower and character flaws. Historically, this was not the case as the burden of disease was that of pestilence and famine. Obesity was therefore viewed as nature's mechanism for storing nutrients [2]. Prior to the twentieth century, excess weight was associated with health, affluence, and strength. Thus, the art, literature, and politics prior to the twentieth century viewed corpulence as a desirable trait. In 1905, Osler described obesity as "morally reprehensible and undesirable" [2]. The Metropolitan Life Insurance Company released a study of mortality between 1911 and 1935, which revealed an association between excess weight and increased early mortality [3]. Thereafter, Freudian psychiatrists of the 1940s described the overweight individual as affective, intensely reactive, and an emotional grown-up child. By the 1960s, the perception was that obesity was undesirable. Perception aside, obesity was linked to both mental and physical health problems [2].

The Growing Obesity Epidemic

Obesity is defined by the World Health Organization and National Institutes of Health using the body mass index (BMI), defined as an individual's mass divided by the square of the height and is universally expressed in kilograms per meters squared (kg/m^2). At its extremes, the classification defines underweight as a BMI of less than $18.5 \, kg/m^2$ and class III obesity as a BMI greater than $40 \, kg/m^2$ (Table 1). A BMI of $>50 \, kg/m^2$ is considered super obesity.

In 1962, approximately 45 % of American adults were obese or overweight. By 2004, approximately 66 % were

Table 1   Classification of obesity using body mass index

Body mass index (kg/m^2)	Interpretation
<18.49	Underweight
18.5–24.9	Normal weight
25–29.9	Overweight[a]
30–34.9	Class I obesity
35–39.9	Class II obesity
>40	Class III obesity
>50	Class IV obesity

[a] Defines obese for Asian population using WHO and NIH scale

obese or overweight [4–6]. Using a BMI $>30 \, kg/m^2$, the prevalence of obesity in America doubled between years 1980 and 2004 [6]. More recent data suggests the prevalence of obesity to be leveling off; however, if one considers that nearly 70 % of the population is overweight or obese, perhaps, we are reaching a "saturation point" where the proportion of the population left to become overweight or obese is indeed genetically protected against adiposity [7, 8]. Despite this leveling off, there is a disproportionate rise in class III obesity. Those with a BMI $>40 \, kg/m^2$ represented 0.9 % of the US population in 1960, whereas they represented 5.1 % of the population in 2004, accounting for nearly 1.5 million adults [4, 6]. Obesity affects some groups more than others. Non-Hispanic Blacks have the highest age-adjusted rates of obesity at 47.8 %, followed by Hispanics at 42.5 %, non-Hispanic Whites at 32.6 %, and non-Hispanic Asians at 10.8 % [9]. Amongst men, obesity prevalence is similar at all income levels. Higher-income women are less likely to have obesity than low-income women. Overall, there is a trend toward less obesity amongst those with college degrees [9, 10].

Pathophysiology of Obesity

How does an individual become obese? Certainly, the laws of thermodynamics require caloric intake to be increased over energy expenditure; however, it is overly simplistic and incorrect to conclude that obesity is a result of increased caloric intake alone. Although obesity is commonly perceived as a lack of willpower and poor lifestyle choices, the pathophysiology is clearly more complex and comprised many factors outside of conscious individual control. The pathophysiology of obesity involves a complex interplay of environmental, genetic factors, and internal factors such as alterations in central nervous system (CNS)-endocrine signals (Fig. 1). First, an obesogenic environment with the intake of energy-dense foods and reduced physical activity contribute significantly to obesity development. High-fructose corn syrup is found in soft drinks and juices; its consumption has increased since 1977, and its use is a risk factor for obesity and hyperlipidemia
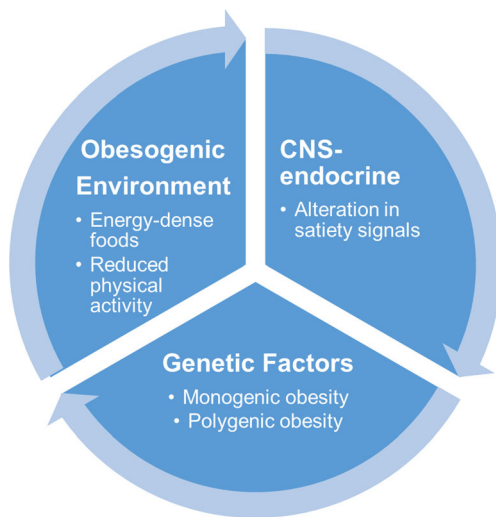
Fig. 1 The complex interplay of obesogenic environment, alterations in CNS-endocrine signaling, and genetic factors leading to obesity. *CNS* central nervous system

[11, 12]. Additionally, fast food is energy dense with a higher proportion of trans-fatty acids (TFAs), which increase the risk of heart disease and obesity [7]. Second, genetic factors such as monogenic and polygenic alterations can lead to genetic syndromes, which have obesity as a central feature. An example of such is Prader-Willi syndrome. Gene mutations can also cause non-syndromic monogenic forms of obesity, such as that leading to leptin deficiency. Leptin deficiency is the only monogenic form of obesity for which successful targeted therapy has been developed [7]. Third, the CNS receives signals from several regulatory loops that help control energy balance. The CNS also receives information about metabolic needs from active tissues such as adipose tissue, liver, stomach, muscle, and bone. Central controls of body weight and appetite involve a complex interplay of satiety and adiposity hormones. When food is consumed, satiety signals such as cholecystokinin (CCK) and glucagon-like peptide-1 are released to reduce oral intake. Although satiation signals are dependent on food intake, hormones promoting hunger are secreted in response to the amount of adipose tissue. Ghrelin is a potent orexigen that stimulates food intake. Satiation signaling is a phasic response, while hunger signaling is a tonic response. An incompletely understood interplay exists between hunger hormones (i.e., ghrelin) and satiety hormones (e.g., insulin, leptin, CCK), which serves to further vary phenotypic expression associated with obesity [7].

The Costs of Obesity

Obesity itself is widely recognized as a disease but is also associated with a wide number of co-morbid conditions [9]. For example, the Prospective Studies Collaboration analyzed 57 prospective studies following 894,000 North American and European adults for a mean of 8 years and demonstrated that every 5 kg/m^2 increase in BMI (between 25 and 50 kg/m^2) was associated with an increased risk for ischemic heart disease [hazard ratio (HR) 1.39, 95 % CI 1.34–1.44], stroke [HR 1.39, 95 % CI 1.31–1.48], and respiratory disease [HR 1.20, 95 % CI 1.07–1.34] [13].

Worse, obesity is associated with an increased risk of all-cause mortality [13–15]. Amongst 3457 Framingham Heart Study participants, obesity was associated with a large decrease in life expectancy and increases in early mortality [15]. Forty-year-old non-smoking men and women with a BMI >30 kg/m^2 lost 7.1 and 5.8 years of life, respectively, compared with 40-year old non-smoking men and women with BMI between 18.5 and 24.9 kg/m^2. Obese adults who smoked lived 13–14 years less than normal-weight non-smokers [15]. During a 10-year follow-up of 4,821,757 person-years, both men and women 50 to 71 years with and without pre-existing disease had an increased risk of death with increasing BMI. The risk of death was consistently higher amongst participants without preexisting chronic disease. In fact, amongst men and women without preexisting disease and a BMI >40 kg/m^2, the multivariate relative risk for death was 2.24 [95 % CI 2.02–2.49], suggesting that obesity itself was associated with a higher risk for death [14].

As a result of the increased morbidity and mortality cost, obesity imposes an economic burden on both public and private payers. Worldwide, obesity absorbs a huge amount of healthcare resources [16]. In the USA, Finkelstein and colleagues used 1998 and 2006 Medical Expenditure Panel Surveys to demonstrate that obese individuals had annual medical spending that was $1429 higher than spending for individuals with normal-range BMI. The annual medical burden of obesity increased from 6.5 % in 1998 to 9.1 % of annual medical spending in 2006. The authors speculated that costs would continue to rise and the costs are generated from treating the diseases promoted by obesity [17].

Challenges Associated With the Critically Ill Obese Patient

Nearly one third of ICU patients are obese [18]. Obesity poses unique physical and non-physical challenges for the ICU team. Physical challenges include difficulty in securing an airway. Compared to the non-obese patient, obese patients have more adipose tissue, resulting in issues with proper positioning and ambiguity in landmark identification. This complicates fundamental resuscitative measures including making bag-mask ventilation, placement of an airway, and intravenous access [19, 20]. Frat et al. compared tracheal intubation and complications between 82 morbidly obese ICU patients (mean 42 ± 6 kg/m^2) to 124 non-obese patients (mean BMI,

24 ± 4 kg/m^2) and demonstrated that the morbidly obese had more difficulty during tracheal intubation (15 versus 6 %) and post-extubation stridor (15 versus 3 %), which were significantly more frequent in obese patients ($p < 0.05$) [21]. The functional residual capacity is reduced in obese patients; thus, long periods of apnea are not well tolerated, leading to atelectasis, hypoxemia, and a greater need for positive end-expiratory pressure (PEEP). Potential consequences of PEEP include reduced venous return and cardiac output. Ventilation may also be more difficult due to baseline chest wall restriction [20]. Additionally, common techniques to gauge volume status, such as bedside ultrasound, may not be feasible, purely due to body habitus. Computed tomography and magnetic resonance imaging commonly have weight limits, limiting their use with increasing obesity. Mobility is impaired and requires both additional support staff and equipment (Fig. 2) [22]. Wound healing may be impaired due to immobility and hyperglycemia, which the obese patient is prone to develop [19].

The non-physical challenges include pharmacologic challenges and nutrition support. The pharmacology of common ICU medications is not well studied in obese patients; thus, dosing common ICU medications poses a unique challenge. The obese patients have greater extracellular volume, greater fat, and greater lean body weight, all of which alter pharmacokinetics [20]. For example, if a larger dose of a lipophilic agent is given, one can anticipate a longer duration of action. Table 2 shows commonly administered ICU medications and suggestions for dosing. Underdosing medications may also be problematic, particularly with antibiotics and anticoagulants [19].

The Obesity Paradox That Occurs in Critical Illness

Even before the onset of critical illness, the obese patient has a baseline increased risk for morbidity and mortality as demonstrated in longitudinal studies. When the obese patient
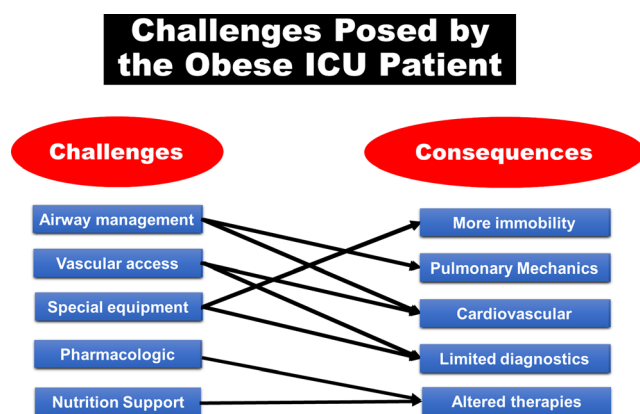
Fig. 2 Challenges and consequences of obesity in the intensive care unit

becomes critically ill, the ICU team is faced with additional challenges, which puts the obese patient at risk for poor outcomes. On the contrary, existing literature suggests that obese patients have improved ICU outcomes. Using data from Medicare claims, Prescott and colleagues demonstrated that obesity was associated with improved mortality among severe sepsis patients [23]. Martino and colleagues evaluated the differences in ICU mortality between extreme obesity (BMI >40 kg/m^2) and normal-range BMI using data from a large international nutrition survey between years 2007 and 2009. Extreme obesity had a lower OR (0.51, 95 % CI 0.27–0.96) for mortality at 60 days, as compared to normal-range BMI (0.84, 95 % CI 0.74–0.94) [24]. Amongst trauma patients, Diaz and colleagues conducted a 4-year single-institution retrospective review and concluded that obesity was not a risk factor for mortality [25]. Several meta-analyses have also suggested improved outcomes amongst critically ill obese patients [26–28]. A recent meta-analysis by Hogue and colleagues of 23 mixed medical-surgical obese patients concluded that obesity was associated with reduced ICU and hospital mortality [27].

Why would obese patients have a survival benefit after critical illness? One hypothesis is that obese individuals have a survival benefit because these patients have nutritional "reserves," which provides substrate during critical illness [7]. A second hypothesis suggests that anti-inflammatory adipokines favorably modulate the inflammatory response. In contrast, leptin and resistin are pro-inflammatory cytokines, which activate macrophages and induced hepatic TNF-α and IL-6, further perpetuating the inflammatory response. Obesity may result in a form of "inflammatory preconditioning" as is seen with ischemic preconditioning in the setting of acute or chronic vasculopathy. In obesity, the baseline inflammation is somehow advantageous in the setting of an acute insult.

It is important to consider methodological limitations of studies evaluating obesity outcomes in critical illness. First, meta-analyses included studies with heterogeneous populations and included studies with missing data [26–28]. Separating medical and surgical populations may yield different outcomes. For example, a higher propensity for procedural intervention in the surgical population may predispose the obese trauma patient to unfavorable outcomes. Indeed, among trauma patients, multiple studies demonstrate an association between obesity and worse outcomes, including mortality [29–34]. Studies of medical ICU patients compared obese (BMI >30 kg/m^2) to non-obese; the latter group included patients who were underweight (BMI <18.5 kg/m^2), a known risk factor for poor outcomes [35, 36]. Third, there was discordance between predicted and observed mortality. In a study by Ray et al, patients had an APACHE II-based predicted mortality of >30 %, but an actual mortality of <10 % [36]. Fourth, obese and non-obese groups were not matched in various studies [35]. Obese patients were younger and had

Table 2 Impact of obesity on drug characteristics

Drug characteristic	Obesity relevance	Examples
Weight-based dosing	Actual versus ideal weight?	Benzodiazepines
Renal metabolism	Increased/decreased GFR	Vancomycin
Hepatic metabolism	Fatty liver and clearance	Phenytoin
Lipophilic	Longer half-life	Propofol, fentanyl
Narrow therapeutic window	Requires closer drug monitoring	LMWHs, phenytoin

Adapted from [17]

GFR glomerular filtration rate, *LMWH* low-molecular-weight heparins

less cancer and HIV, as compared to the non-obese [35–37]. These confounders could help to explain the discrepancies observed when reviewing available literature.

Can all obesity be equally categorized using the BMI? The sagittal abdominal diameter (SAD) is another marker for obesity. SAD is the vertical distance from the iliac crest to the tip of the umbilicus. An SAD of 26 cm represents the 75th percentile. In a prospective study of 403 obese patients across two centers in France, Paolini and colleagues compared the association between SAD and mortality. Abdominal obesity, as measured by SAD, was associated with a greater risk for mortality (adjusted odds ratio, 2.12; 95 % confidence interval, 1.25–3.60), abdominal compartment syndrome, and venous thromboembolic disease. The authors concluded that central adiposity is a better indicator for outcomes, and its measurement is better reflected by the SAD, as compared to BMI [38]. In a cohort of 240 trauma patients, Joseph and colleagues demonstrated a waist to hip ratio of 1 or greater independently predicted mortality and complications better than BMI [39].

Can two patients with an equivalent BMI have different phenotypes? Sarcopenia is defined as a reduction in muscle mass less than 2 standard deviations to that of a normal healthy individual and is commonly evaluated using computerized tomography (CT) imaging of the psoas muscle at the L3 level [40]. Sarcopenia is different than cachexia in that weight loss is not compulsory in sarcopenia (Table 3). Figure 3 demonstrates that a patient with a BMI of 17.5 kg/m^2 has significantly greater skeletal muscle mass when compared to the patient with a BMI of 38 kg/m^2 [41••]. Sarcopenia is associated with worse outcomes in cancer patients. In a study of 325 obese patients with gastrointestinal and solid tumors, Prado and colleagues demonstrated that sarcopenic obesity was associated with poor functional status and increased mortality. The authors hypothesized that chemotherapy was less utilized

in cancer patients with sarcopenia [38]. The (hidden) sarcopenia represents a different phenotype, which is underrecognized and may have implications for outcomes in critically ill obese patients [42].
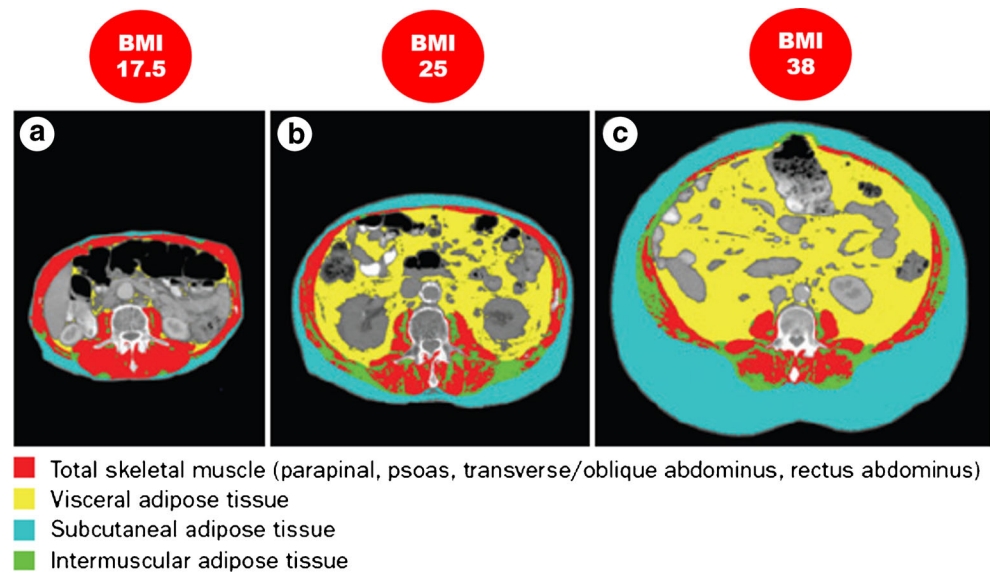
Nutrition Support in the Critically Ill Obese Patient

Determining caloric requirements can be challenging in obese patients. Using 25–30 kcal (kg) per actual or ideal body weight (in kg) may lead to overfeeding or underfeeding. Predictive equations such as Harris-Benedict are not accurate for estimating REE in critically ill patients and were not validated in severe obesity [43]. The Ireton-Jones equation does take into account obesity but is not validated for mechanically ventilated critical care patients [44]. When available, indirect calorimetry (IC) should be used to determine energy requirements. IC is the most accurate method for determining energy expenditure; however, its use is limited by cost and required clinical expertise for interpretation. When patients do not meet valid testing criteria or IC is not available, the Penn State University (PSU) predictive equation most accurately predicts REE as compared to Harris-Benedict, Mifflin-St. Jeor, Swinamer, and Ireton-Jones. Amongst critically ill obese patients with a BMI ≥45 kg/m^2, the PSU equation was found to have the highest prediction accuracy at 76 % (±10 % of REE), as compared to other equations [45, 46••]. In adults ≥60 years with a BMI ≥30 kg/m^2, a modified PSU was more accurate than unmodified PSU (70 versus 58 % accuracy, $p = 0.04$) [47]. Even IC has high variability in measuring energy expenditure for ICU patients with a BMI >50 kg/m^2 [48].

Table 3 Key differences between sarcopenia and cachexia

Sarcopenia	Cachexia
Weight loss *not* compulsory	Weight loss is compulsory
Muscle loss and function compulsory	Muscle loss and function *not* compulsory
Age or disease related	Chronic disease
Low-grade inflammation	Moderate- to high-grade inflammation

Fig. 3 Computerized tomography (CT) imaging of the psoas muscle at the L3 level demonstrating the proportion of skeletal muscle to adipose tissue. Note that **b** has a normal BMI of 25 kg/m^2, but increased intermuscular adipose tissue as compared to **a** with a BMI of 17.5 kg/m^2. *BMI* body mass index in kilograms per meters squared. Reprinted from [41••] by permission of Nature Reviews Clinical Oncology

■ Total skeletal muscle (parapinal, psoas, transverse/oblique abdominus, rectus abdominus)
■ Visceral adipose tissue
■ Subcutaneal adipose tissue
■ Intermuscular adipose tissue

Among the three major critical care nutrition support guidelines, only the joint American Society of Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) 2016 guideline provides a specific recommendation for nutrition support for the critically ill obese patient (Table 4) [49, 50, 51••]. The ASPEN/SCCM guideline recommends that goal feeding should not exceed 65–70 % energy requirements, calculated using 11–14 kcal per actual body weight for patients with BMI in the range of 30–50 kg/m^2 or 22–25 kcal per ideal body weight (IBW) for patients with BMI >50 kg/m^2 while providing protein 2.0–2.5 g/kg IBW [51••].

The first three studies of hypocaloric nutrition support in obese patients included less than 30 non-ICU obese patients. All three of these studies used parenteral nutrition (PN) [52–54]. Dickerson et al.'s work was the first study evaluating hypocaloric enteral nutrition (EN) in critically ill obese patients [55]. Forty obese trauma patients who received EN for at least 7 days were reviewed, comparing those who received hypocaloric (<20 kcal/IBW/day) to full EN support (>20 kcal/IBW/day) with both groups receiving high protein (2 g/IBW/day). The authors concluded

that the full-feeding group had longer ICU days, longer duration of mechanical ventilation, and more antibiotic days [55]. Limitations include that this was a small retrospective study. Second, the hypocaloric group (as compared to the full EN group) had a higher BMI (41 versus 36 kg/m^2). Third, the full-feeding group received 30 kcal/IBW/day of EN, which is considered hyper-alimentation. Fourth, prescribed caloric goals were not reached in the hypocaloric group, perhaps as a result of selection bias leading to iatrogenic hypocaloric feeding. Lastly, all were trauma patients, limiting external generalizability [55]. Dickerson et al. re-visited hypocaloric EN in the obese, studying it in young (<60 years old) versus older (>60 years old). Seventy-eight trauma patients were retrospectively evaluated. There was an improved survival in obese patients receiving 18 kcal/IBW/day compared to those receiving 21 kcal/IBW/day (85 versus 95 % survival). Limitations of this study included its small retrospective nature, the older group received more PN (37 versus 10 %), ventilator-associated pneumonia rate was >40 % in each group, and all were trauma patients (limiting external generalizability) [56].

Table 4 Recommendations for nutrition support in critically ill obese patients

Guideline	Recommendations for nutrition support in the critically ill obese
2009 ESPEN Critical Care Guidelines	No specific recommendation
2015 Canadian Critical Care Nutrition Guidelines	No specific recommendation
2016 ASPEN/SCCM Critical Care Nutrition Guidelines	The goal of the EN regimen should not exceed 65–70 % of target energy requirements or 11–14 kcal/kg ABW per day in those with BMI 30–50 kg/m^2 or 22–25 kcal/kg IBW per day in those with a BMI >50 kg/m^2 while providing protein 2.0–2.5 g/kg IBW

ABW actual body weight, *ASPEN* American Society of Parental and Enteral Nutrition, *BMI* body mass index, *EN* enteral nutrition, *ESPEN* European Society of Parental and Enteral Nutrition, *IBW* ideal body weight

There are no randomized controlled trials of hypocaloric high-protein versus eucaloric feeding in critically ill obese patients. The small non-randomized studies with contemporaneous controls led to a grade D recommendation for high-protein hypocaloric nutrition in critically ill obese patients [51••]. Application of this recommendation must be done with caution. For example, the notion that obese patients cannot be malnourished is a fallacy. The malnourished obese patient may benefit from both calorie and protein optimization. Next, sarcopenic obesity in critical illness is not well studied. A better understanding, including outcomes, of this subset of obese patients may have implications for energy and protein goals. Extrapolation of recommendations toward the obese medical critical care patient should be done with caution as hypocaloric EN in this patient population has not been well studied.

Conclusions

Obesity is a chronic disease and places the individual at risk for additional disease acquisition. The prevalence of obesity is increasing, and the pathophysiology is a complex interplay of genetics, obesogenic environment, and neuroendocrine signaling. One third of all critically ill obese patients are obese, and knowledge of the disease process along with a multi-disciplinary approach will be the key to understand and mitigate the numerous physical and non-physical challenges. The available outcome data of critically ill obese suggests that the obese critically ill patient has improved outcomes as compared to the non-obese critically ill patient, termed the critical care obesity paradox. This should be viewed through a skeptical lens with a thorough understanding of methodological limitations including patient heterogeneity and the drawbacks of BMI as the sole classifier of obesity. Nutrition support of the obese ICU patient requires careful assessment of risk factors for malnutrition, assessment of caloric needs, and consideration for hypocaloric nutrition with protein optimization in selected individuals. Additional prospective studies are needed to provide more definitive recommendations for high-protein hypocaloric nutrition.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:

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