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OBESITY AND NUTRITION IN ARDS

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Abstract

This chapter collectively discusses two important topics related to patients with ARDS: 1) obesity and its potential contribution to clinical outcomes through proposed biologic mechanisms and 2) current literature on provision of nutrition and micronutrients. The prevalence of obesity is rapidly increasing around the world, and more than one third of Americans are now obese. While obesity is associated with increased morbidity and mortality in the general population, recent literature suggests that among critically ill patients including those with ARDS, the relationship between obesity and outcomes is quite complex. Observational data demonstrate that obese patients may be at greater risk of developing ARDS and of having longer ICU and hospital lengths of stay compared to normal weight patients. However, obesity is also associated with improved survival. Therefore, in contrast to what might be assumed by clinicians, although obesity may confer greater ICU morbidity, it appears to simultaneously decrease mortality. The mechanisms for these findings are not yet clear, but recent biologic data may begin to provide an explanation.

Critical illness, and more specifically the acute respiratory distress syndrome (ARDS), is a catabolic state where patients demonstrate a profound inflammatory response, multiple organ dysfunction, and hypermetabolism. This is often accompanied by malnutrition, which can lead to further impairment of immune function and increased morbidity and mortality in critically ill patients. Over the past decade or more, as we have come to better understand immunologic effects of nutrition in critical illness, nutrition has begun to be thought of as therapeutic, rather than purely supportive. Additionally, the concept of pharmaconutrition has emerged. Fortunately, several recent large studies about nutrition in critical care, with some investigations specifically in patients with ARDS, have provided valuable new evidence.

Keywords

ARDS; acute lung injury; obesity; nutrition; enteral nutrition; parenteral nutrition

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OBESITY AND ARDS

The prevalence of obesity, especially extreme obesity (BMI $\geq 40\text{kg/m}^2$), has been rapidly increasing for the past two decades in the US and other developed countries ¹. Over one third of the American population is obese, and over 5% is extremely obese ². The public health consequences of this rise in obesity are considerable, as obesity is associated with significant morbidities and increased all-cause mortality in both men and women ¹. However, in critically ill patients including those with ARDS, the relationship between obesity and morbidity and mortality appears to be more complex and at times counterintuitive. A decade of observational evidence suggests that obese patients may be at greater risk of developing ARDS and other organ failures in the intensive care unit (ICU), and of having protracted ICU and hospital lengths of stay (LOS) compared to normal weight patients. Yet, obese patients appear to have greater survival rates compared to similarly ill lean patients. Therefore, in contrast to what might be assumed by clinicians, although obesity may confer greater ICU morbidity, it appears to simultaneously decrease mortality. The mechanisms for these findings are not yet clear, but recent biologic data may begin to provide an explanation.

CLINICAL COURSE AND OUTCOMES OF ARDS IN OBESE PATIENTS

Studies in ARDS and General Critical Illness: Risk—Although the protective effects of diabetes against the development of ARDS were first demonstrated 15 years ago ³, little has been reported on the effects of obesity and other components of the metabolic syndrome on the development of ARDS. Obesity-associated co-morbid illnesses such as cardiovascular disease undoubtedly increase the overall risk of developing critical illness, and recent studies have suggested that the obese are at elevated risk for critical illness from infectious etiologies, such as the H1N1 influenza virus ⁴. However, obesity's effects on the relative risk of developing ARDS, independent of comorbid conditions and other confounding factors, have only recently been examined. Work by Gong and colleagues examining a cohort of critically ill patients at risk for ARDS suggests that the risk of developing ARDS rises with BMI ⁵ independent of severity illness, gender, diabetic status, or identified risk factor for ARDS. Obese BMI categories were associated with the development of ARDS compared with normal weight, with adjusted OR of 1.66 (95% CI 1.21 to 2.28) for obese and 1.78 (95% CI 1.12 to 2.92) for severely obese. Additional work by this group has shown a similar association between BMI and the risk for acute kidney injury (AKI) in patients with ARDS ⁶. Interestingly, this latter study also demonstrated an association between elevated BMI and *decreased* 60 day mortality in patients with ARDS and AKI.

Studies in ARDS and General Critical Illness: Outcomes—Over the last decade, a growing number of observational studies have shown that despite having elevated risks for the development of ARDS and other organ failures, obese critically ill patients paradoxically have similar to significantly *improved* survival compared to normal weight critically ill patients ^{7–24}. Although the majority of these reports have included general medical, surgical, and trauma ICU patients, several prior studies have specifically focused on ARDS ^{5–6,10,17–18,25}.

Of these reports, most were performed as secondary analyses of other studies of ARDS, including the Molecular Epidemiology of ARDS study⁵⁻⁶, ARDS Network ARMA and ALVEOLI trials^{17,25}, and King County Lung Injury Project (KCLIP) in Seattle¹⁸, and one was an observational study utilizing the Project Impact® database¹⁰. All but one¹⁷ of these reports showed a significant association between BMI and ARDS mortality at their respective endpoints (ICU, hospital, or 28–90 days) in unadjusted analyses, in which mortality fell with rising BMI. The association between BMI and mortality was maintained after multivariate analyses in two of these studies^{6,17}, in which the overweight and obese subjects were found to have reduced mortality compared to normal weight subjects, except possibly for those with a BMI > 50 kg/m²¹⁰ – suggesting a ‘J-curve’ relationship between BMI and mortality. Three studies^{5,10,18} also examined length of stay and discharge disposition in their cohorts. Of these, two showed significant associations between rising BMI and the duration of mechanical ventilation, ICU and hospital lengths of stay, and the likelihood of subsequent discharge to a rehabilitation or skilled nursing facility^{5,18}. Though in aggregate these studies do not yield a clear picture of BMI’s effects on mortality, it is worth noting that the studies finding either no association between BMI and mortality or a loss of such association after multivariate analyses examined cohorts with relatively lower mean BMIs compared to the studies that showed significant associations. Thus, what can be surmised to date is that obesity has consistently been shown not to increase the risk of death from ARDS, and may even be protective in this disease.

In addition to these studies and many others that have examined general ICU patients, three meta-analyses^{26–28} and a large observational study of outcomes in obese critically ill patients²³ have recently been published. The meta-analyses included 62,000 to 88,000 subjects from up to 22 published studies and found that critically ill overweight and obese subjects had significantly lower hospital mortality compared to normal weight subjects. The Dutch National Intensive Care Evaluation (NICE) observational study examined over 154,000 critically ill patients from 1999 to 2010 and found a significant association between BMI and mortality, with an adjusted OR that ranged from 0.86 to 0.96 in the overweight, obese, and severely obese BMI categories using a reference BMI of 25, while the OR_{adj} for subjects in the normal BMI range was 1.07. As seen in several other studies, a slight upslope in mortality (‘J curve’) was noted as BMI rose above 40 kg/m² in this study, but it remained below that seen in the normal BMI range.

In summary, current evidence suggests that overweight, obese and extremely obese critically ill patients may be at higher risk for the development of ARDS and may experience greater associated morbidity including ICU length of stay and duration of mechanical ventilation with ARDS; yet these same patients appear to have equal to lower mortality from ARDS compared to normal weight patients (Box 3).

Limitations of Prior Investigations—There are several limitations to prior studies in outcomes in critically ill patients with and without ARDS. First, BMI has been used in all studies as the measure of obesity, but it may not accurately reflect obesity syndromes compared with other measurements, such as waist circumference²⁹. Furthermore, measurement of BMI may be altered by intravenous fluid administration in ICU patients before weight is obtained or erroneous assessment of height in supine critically ill

patients³⁰. Third, a tool for assessing severity of illness specifically in obese patients does not exist and current assessment tools, including APACHE and SAPS^{31–32}, may not accurately reflect mortality risk in obese patients due to unknown factors that may be specific to the obese population. Fourth, processes of care for obese and extremely obese patients in different hospitals and ICUs are likely to be highly variable and may bias results, either toward improved or worse outcomes for obese patients³³. Finally, diagnosing ARDS and assessing the degree of critical illness in extremely obese patients can be very difficult (e.g. measuring noninvasive blood pressure measurements³⁴ or interpreting of chest radiographs), thus leading to misclassification and incorrect case ascertainment, although many studies report an improvement in outcomes in the overweight and obese groups where such misclassification is less likely²⁵. However, the study of critically ill patients at risk for ARDS by Gong, et al, found that increasing BMI was significantly associated with the subsequent development of ARDS due to a greater incidence of hypoxemic respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio < 200) and not a greater incidence of bilateral pulmonary infiltrates on chest radiograph. Thus, misinterpretation of chest radiographs in obese patients is unlikely to be responsible for incorrect ascertainment⁵.

Possible Explanation of Findings—Results of the above clinical studies have now prompted interest in investigating mechanisms by which obesity may influence ICU course and outcomes. Reasons for increased duration of mechanical ventilation and ICU LOS in obese patients with ARDS observed in some studies may be due to physiologic factors that lead to longer duration of care but do not increase mortality. For example, lung derecruitment due to the weight of the abdomen and chest wall and provider reluctance to extubate an extremely obese patient may contribute to longer duration of ventilation³⁵.

However, explanations of why the incidence of ARDS may be higher, yet survival better in obese patients compared to normal weight patients are less clear. It is possible that the obese may be ‘primed’ for the development of ARDS through baseline low grade inflammation and vascular activation and injury^{36–37}, yet the subsequent sustained inflammation of ARDS is curtailed by as of yet unknown factors. In support of this, a recent study found that obese patients with established ARDS have higher levels of circulating von Willebrand factor, thought to be a marker of vascular injury, yet lower levels of proinflammatory cytokines (IL-6, IL-8) and surfactant protein D (a marker of alveolar epithelial injury) that are known to be increased in ARDS and to be associated with increased mortality²⁵, thus suggesting that innate immunity and the inflammatory response may be altered in obesity.

BIOLOGIC RELATIONSHIP OF OBESITY AND ARDS

Obesity and the pathogenesis of ARDS—Despite decades of research, the pathogenesis of ARDS remains incompletely understood. It is increasingly recognized, however, that ARDS pathogenesis and outcome may be influenced by host factors, including genetic polymorphisms and co-morbid conditions^{38–39}. In this light, the clinical evidence that obesity may both promote and ameliorate ARDS suggests obesity may be one such factor. In the case of ARDS promotion, such an interaction would not be surprising, as obesity is itself believed to be an inflammatory state with baseline increased circulating neutrophil levels^{40–41}, elevations in blood TNF α (alpha), IL-1 β (beta), IL-6, and IL-8^{42–43},

and innate immune cell activation^{44–46} with endothelial injury^{47–49}, perhaps predictive of inflammatory synergy between the obese state and inciters of ARDS. However, evidence that plasma IL-6 and IL-8 fall with rising BMI in ARDS patients²⁵, suggest that although obesity may increase the risk of *developing* ARDS⁵, it may paradoxically have an *attenuating* effect on ARDS-associated inflammation and hence the progression of the disease.

Although human studies examining the effects of obesity on ARDS pathophysiology are scarce, recent reports in animal models suggest that such models may recapitulate the clinical effects of obesity, allowing further dissection of the underlying mechanisms. Most animal studies examining obesity-associated effects on pulmonary immunity and inflammation have focused on models of asthma and pneumonia, and although some forms of airway inflammation appear to be amplified by obesity⁵⁰, the response to pneumonia is blunted^{51–53}, suggesting that the inflammatory response in the alveoli (the site of ARDS) is impaired. In the published reports examining obesity's effects on ARDS models, obese mice and rats demonstrate reduced inflammation, lung injury, and mortality from LPS-, hyperoxia-, and ozone-induced ARDS^{54–58}, although in the case of ozone exposure, findings are mixed and appear to vary with the acuity of exposure^{57,59–60}.

Obesity and its effects on the inflammatory response in ARDS—Given the systemic abnormalities associated with obesity and the accompanying metabolic syndrome, obesity's effects on the pathogenesis of ARDS almost certainly reflect interaction between multiple facets of the obese state. Although few reports focus on obesity itself, a growing literature examines the effects of the metabolic syndrome on ARDS pathogenesis and outcome. The most extensively investigated element of the metabolic syndrome in this regard is diabetes.

Diabetes has been convincingly shown to be associated with a reduced risk of developing ARDS in four large clinical studies of high risk patients including those with sepsis, aspiration, trauma, and massive transfusion, with an adjusted odds ratios ranging from 0.33 – 0.76^{3,61–63}. Although this protective effect is reproducible in animal models of diabetes^{54,64–66}, the underlying mechanisms remain unclear. Diabetes is associated with impaired innate immune response^{67–68}, which although believed to drive the increased risk of infection in diabetics through impairment of neutrophil function among other effects,⁶⁹ might conversely attenuate inappropriate inflammatory states such as ARDS. Evidence supporting roles for either hyperglycemia or insulin resistance in the attenuation of ARDS is conflicting, but a recent study has suggested that the protective effects of occur in both type 1 and 2 diabetes and are independent of diabetic therapy usage⁶³. Interestingly, diabetic status was not associated with change in mortality in any of the four studies.

Comparable studies investigating dyslipidemia and its effects on ARDS risk and pathogenesis have not yet been published. However, as with obesity in general, dyslipidemia is associated with baseline elevations in circulating neutrophil levels in both humans and mouse models, often in the absence of accompanying obesity^{70–73}. Persistent activation of both monocytes and neutrophils are described in dyslipidemic states, accompanied by endothelial injury⁷⁴, and may be driven by direct effects of lipid species on

leukocytes^{75–77}. Yet, in this setting there appear to be defects in neutrophil and monocyte function^{78–79}, and recently animal models of hypercholesterolemia without obesity have suggested that the development of LPS-induced ARDS is blunted⁸⁰ and that neutrophil chemotaxis and pulmonary macrophage activation are impaired in this model.⁵⁸ Whether such defects might reflect tonic activation of the innate immune system with ‘desensitization’ to acute stimuli or other effects of the dyslipidemic state is not yet known.

Another significant feature of the metabolic syndrome and obesity in general is the dysregulation of adipokine release and response. Although initially described as hormone-like signaling molecules released by adipose tissue and involved in metabolic homeostasis, adipokines such as leptin, adiponectin, and visfatin have recently been shown to have quite protean effects including modulation of both innate and adaptive immune systems^{81–82}. The best studied of these molecules is leptin, which was originally described as a regulator of appetite. Leptin has been shown to be important in the marrow development of the myelomonocytic lineages^{83–84}, and to serve as an activation and survival signal for neutrophils in the periphery^{85–87}. Interestingly, leptin also appears to act as a neutrophil chemoattractant^{88–91} and may be released by the injured lung^{91–93}, while serum levels of leptin are elevated in critical illness^{94–96}. These findings, together with recent animal and human studies^{91,97}, suggest a possible role for leptin in the development and progression of ARDS, and thus leptin-resistance, as occurs in obesity, might yield a protective effect.

How leptin’s effects on innate immune function may be altered in obesity is poorly understood. Obesity is typically accompanied by a state of hyperleptinemic leptin resistance in which leptin response is blunted despite high circulating levels of this cytokine, presumably due to receptor desensitization. Elevated leptin levels in patients with end-stage renal disease have been implicated in the neutrophil dysfunction that accompanies that state⁹⁰, while animal models of aleptinemia and leptin-resistance suggest that the development of hyperoxic and LPS-induced ARDS is blunted in this setting^{55–56,91}. Whether hyperleptinemia with leptin resistance may affect the development of human ARDS has not yet been addressed.

Obesity and its effects on pulmonary mechanics in ARDS—One further possibility that must be considered when examining the potential interaction between obesity and ARDS focuses on the biomechanical effects of obesity. Obese individuals manifest altered pulmonary mechanics compared to lean individuals, at baseline and when mechanically ventilated (Figure 1). Obese patients with ARDS demonstrate similar changes, with a combination of reduced chest wall and lung compliance leading to a lower FRC and consequently atelectasis, increased airways resistance and closure, and ventilation/perfusion mismatch^{98–99}. Although these changes likely underlie obesity-associated delays in liberation from mechanical ventilation, how such alterations might be protective in ARDS are unclear.

It is possible that the combination of lower respiratory system compliance and higher airways resistance, which yield atelectasis and higher static and dynamic airway pressures for a given tidal volume, may prompt clinicians to selectively increase PEEP and decrease tidal volumes in the obese, thus mimicking or accentuating a protective low tidal volume

strategy. However, it has been shown that obese ARDS patients are typically ventilated at higher tidal volumes (cc/kg ideal body weight) than normal weight patients^{17–18}, indicating that, in light of comparable to improved survival in the obese, mechanical ventilation (even at higher tidal volumes) may be better tolerated in these patients. Furthermore, although overall mortality in the RCT of low tidal volume ventilation in ARDS was not different between lean and obese patients¹⁷, data from this study suggest that obese patients may have tolerated higher tidal volumes (12 cc/kg IBW) better than did lean patients. The relative reduction in mortality attributable to lower tidal volumes (6 cc/kg IBW) in the overall cohort was 30%, yet when stratified into normal, overweight, and obese BMI categories, the relative reductions in mortality between high and low tidal volume arms of the study were 42%, 27%, and 12%, respectively, although this finding did not reach statistical significance. Thus, obese patients may be less susceptible to VILI. Whether this might be related to the mechanical interaction between obese patients and ventilation or an additional manifestation of attenuated inflammatory response in obese ARDS has yet to be examined.

In reviewing the literature describing the many effects of obesity and the metabolic syndrome, it is important to emphasize that both human and, with rare exceptions, animal studies examining ‘discrete’ elements of obesity and the metabolic syndrome have not examined these in isolation of obesity or the other facets of the syndrome. For instance, only one of the reported clinical studies on diabetes and ARDS included BMI as a confounding variable, and the db/db mouse model, although used in various studies to specifically examine leptin resistance, diabetes, or obesity, is also noted to be extremely dyslipidemic. Furthermore, until the recent study of Gong and colleagues,⁶³ none of the published studies examining the effects of diabetes on ARDS risk included BMI as a potential confounding factor, and none has yet to include measures of dyslipidemia. Thus, it remains unclear which elements of obesity and the metabolic syndrome may be operative in the majority of reported findings but several are plausible (Figure 2).

CLINICAL RECOMMENDATIONS ON CARING FOR OBESE ARDS PATIENTS

Caring for critically ill obese and severely obese patients in a clinical setting can be challenging. Like all ICU patients, special attention should be paid to prevention of infection with measures such as the use of a checklist during central line insertion to prevent central line associated blood stream infection¹⁰⁰ and semi-recumbent positioning to prevent ventilator associated pneumonia¹⁰¹.

Prior studies have also suggested that obese patients who are mechanically ventilated receive tidal volumes early in their ICU course substantially greater than the 6cc/kg predicted body weight shown to improve survival^{18,25,102}. ICU clinicians should therefore be conscientious when choosing tidal volumes in obese patients. Furthermore, the recumbent position leads to increased atelectasis and greater mechanical loading of the diaphragm in obesity, contributing to hypoxia and difficulty weaning. Therefore, consideration should be given to positioning obese patients as upright (45°) as safely possible and transitioning to chair during weans, both of which have been shown to improve mechanics in these patients¹⁰³. Lastly, the pharmacokinetics and pharmacodynamics of many drugs commonly

used in critical illness are substantially altered in obese and severely obese patients compared with those of normal weight (e.g. heparin and benzodiazepines); attention to detail when using these medicines is important (Box 1).

CONCLUSIONS: OBESITY AND ARDS

Survival in the general population is j-shaped, with increased mortality in underweight people, lowest mortality in patients with a BMI near 25kg/m², and increasing mortality rates in overweight, obese, and extremely obese patients^{1,104}. Evidence in critically ill patients, however, suggests that overweight, obese and extremely obese patients have lower mortality compared to normal weight patients. The limited studies of obese patients published to date show that rising BMI may increase the risk for the development of ARDS, but paradoxically does not increase mortality from this disease, and may in fact be protective. Health professionals may assume that obese patients have worse survival and morbidity due to presumed difficulties of caring for such critically ill patients including transport, body positioning, intravascular access, diagnostic imaging, and ventilator weaning. While the literature does suggest that obese patients may have longer durations of ventilation and ICU lengths of stay, their survival is at least as good as normal weight patients. This information is important for clinicians to recognize when discussing prognosis and expectations with critically ill patients and their families.

NUTRITION IN PATIENTS WITH ARDS

Critical illness, and more specifically the acute respiratory distress syndrome (ARDS), is a catabolically stressed state where patients demonstrate a systemic inflammatory response, multiple organ dysfunction, hypermetabolism, infectious complications, and malnutrition.¹⁰⁵ Malnutrition is coupled with impairment of immune function and increased morbidity and mortality in critically ill patients.¹⁰⁶ Over the past decade or more, as we have come to better understand immunologic effects of nutrition in critical illness, nutrition has begun to be thought of as therapeutic, rather than purely supportive. Additionally, the concept of pharmaconutrition, or the delivery of specific nutrients with potential immunomodulating properties, has emerged. Fortunately, several recent large studies about nutrition in critical care, with some investigations specifically in patients with ARDS, have provided valuable new evidence.

ENTERAL VERSUS PARENTERAL NUTRITION

Enteral nutrition (EN) is the standard of care in patients with ARDS and should be initiated preferentially over parenteral nutrition (PN) unless there is a known contraindication to EN such as ischemic bowel, intestinal obstruction, severe malabsorption, and severe short gut syndrome. Several randomized control trials (RCTs) have compared EN to PN in critically ill patients with an intact gastrointestinal (GI) tract, and when these data were aggregated in meta-analyses, there was no difference in survival.^{107–109} However, EN is associated with a significant reduction in infectious complications (relative risk 0.58, 95% confidence interval [CI] 0.41–0.80), in addition to being less expensive than PN. Data also suggest that lack of use of the GI tract rapidly leads to atrophy of gut luminal mucosa, and this may increase bacterial translocation across the wall of the gut into the bloodstream.¹¹⁰ Even small

amounts of EN, called trophic feedings, increase blood flow to the GI tract and preserve GI epithelium, and EN may also improve overall immune function by supporting gut-associated lymphoid tissue (GALT).¹¹¹

EARLY VERSUS DELAYED NUTRITION

Early EN is most often defined as being initiated within 48 h of ICU admission. Many prior RCTs have compared early EN versus delayed nutrient intake in mechanically ventilated critically ill patients, and when these results were meta-analyzed, early EN was associated with a trend towards mortality reduction (RR=0.75, 95% CI 0.50–1.04, p=0.08) and a significant reduction in infectious complications (RR=0.81, 95% CI 0.68–0.97, p=0.02).¹¹² The provision of early EN does not seem to be associated with duration of mechanical ventilation or ICU length of stay. There have been 6 studies that have investigated EN versus no EN or IV fluids alone, and when these data are aggregated, the trends in reduction of mortality (RR=0.62, 95% CI 0.37–1.05, p=0.08) and infectious complications (RR=0.70, 95% CI 0.48–1.02, p=0.06) hold. Thus, these data suggest that EN should be initiated in critically ill patients with ARDS within 48 hours of ICU admission unless there is an absolute contraindication to EN.

Ischemic bowel has been reported as a very rare complication of EN in critically ill patients and can be fatal. Recent guidelines therefore recommend that EN be avoided when patients are in shock or being actively resuscitated, when vasopressors are being initiated, or when vasopressor doses are increasing.¹¹³ However, a recent well done large observational study of 1174 mechanically ventilated patients receiving vasopressors found that early EN (initiated < 48 hours after ICU admission) was associated with reduced hospital mortality (OR=0.65, 95% CI 0.48–0.89) and hazard of death (HR=0.70, 95% CI 0.56–0.88) after adjustment for severity of illness (Acute Physiologic and Chronic Health Evaluation Score), age, sex, standardized mortality ratio, race, source of admission, and admitting diagnosis.¹¹⁴ After propensity matching, hospital mortality was still significantly lower in the early EN group. These new data suggest that initiating EN early is safe even in patients receiving vasopressors, but care should be taken in patients who are in shock and being aggressively resuscitated.

CALORIC PRESCRIPTION OF ENTERAL NUTRITION

The above data suggest that EN, preferentially over PN, should be started early in critically ill patients with ARDS, but they do not inform the questions of how many calories patients should receive or whether supplemental PN should be used to meet caloric requirement. Fortunately, several large RCTs in critically ill patients discussed below have shed more light on these issues. Energy expenditure is variable and depends on age, gender, body mass, and type and severity of illness. In critically ill patients, total energy expenditure (TEE) can be measured with indirect calorimetry. However, in clinical practice, resting energy expenditure (REE) is usually estimated using a variety of available equations and is then multiplied by a “stress factor” of 1.0–2.0 to estimate TEE (and therefore caloric requirements). Roughly 25 kcal/kg ideal body weight is frequently the standard practice, and other equations such as Harris-Benedict, Ireton-Jones, and Weir are commonly used (Table).

Predictive equations, however, tend to be inaccurate,¹¹⁵ and furthermore, data do not suggest that precise estimation of caloric need is associated with improved outcomes.

The National Heart Lung and Blood Institute's ARDS Network recently published a large RCT of trophic enteral feeding vs full enteral feeding.¹¹⁶ Prior to this study, literature on hypocaloric feeding in critically ill patients had been largely observational and found contradictory results. For example, one study found that a greater cumulative caloric deficit was associated with worse clinical outcomes,¹¹⁷ while another observational study demonstrated that ICU patients who received from 33–66% of their caloric goal had better clinical outcomes than those patients who received 67–100% of their goal.¹¹⁸ In the ARDS Network trophic feeding study, 1000 adults with ARDS for less than 48 hours were randomized to receive either 10–20kcal/hr or full calorie enteral feeding for the first 6 days after enrollment, followed by full enteral feeding in all patients. Participants were relatively young (mean of 52 years) and obese (mean BMI of approximately 30kg/m²). The trophic group received approximately 400kcal/day for the first 6 days, while the full feeding group received 1300kcal/day. There were no differences in the primary outcome of ventilator-free days between the trophic and full feeding groups (14.9 [95% CI 13.9–15.9] and 15.0 [95% CI 14.1–15.9], $p=0.81$). Mortality at 60 days (23.3% vs. 22.2%, $p=0.77$), organ-failure free days, and infectious complications were also not different between the two groups.

In addition to participants in this trophic feeding study being relatively young and well-nourished, one additional criticism of this trial was that it did not examine long-term outcomes, so any deleterious effect of trophic feeding after hospitalization would have been unknown. In response, two studies examining long-term outcomes in surviving participants of the trophic feeding trial have recently been published, and both suggest that trophic feeding in these patients has no long-term untoward effects. In the first study, the authors used several survey instruments administered over the phone or by mail to assess physical function, mental health, quality of life, anxiety, depression, PTSD, cognition, and employment at 6 ($n=525$) and 12 ($n=508$) months after randomization in the trophic feeding RCT.¹¹⁹ Patients who were cognitively impaired at baseline, homeless, non-English speaking, or <18 years old were excluded. There was no difference in survival at 12 months (65% of trophic group vs. 63% of full feeding group, $p=0.63$). Physical function at 12 months (the primary outcome) was not different between the trophic and full feeding groups, and the vast majority of hypothesis-generating secondary outcome analyses also found no difference between groups. Because self-reported outcomes may differ from those actually measured, in the second study the same authors also examined a smaller sample of 174 surviving participants of the trophic feeding trial to determine their in-person physical and cognitive performance.¹²⁰ Six-minute walk test (6MWT), 4-minute timed walk speed, manual muscle testing, hand grip strength, maximum inspiratory pressure (MIP), FEV1, FVC, BMI, arm anthropometrics, and a battery of cognitive tests evaluating executive function, language, memory, verbal reasoning, and attention were all measured at 6 and 12 months after ARDS onset by blinded research personnel. None of the physical or cognitive outcomes measured at 6 and 12 months were different between participants in the trophic and full feeding groups, even after adjustment for nonsignificant baseline differences in multivariable analyses. The above new studies of early trophic versus full enteral feedings in patients with ARDS suggest that either approach is reasonable in patients who are relatively

well-nourished and young. Data on caloric prescription for malnourished patients are sparse, and these patients should probably receive full calorie feedings until further research is available.

MONITORING OF ENTERAL NUTRITION

Given the frequency of gastric dysmotility in critically ill patients, it became common practice over the past several decades to frequently monitor tolerance of enteral feeding by checking gastric residual volumes (GRV), especially in the first few days after initiating enteral feedings. However, lower GRV thresholds result in delivery of less enteral nutrition due to frequent interruptions and are not associated with less vomiting, aspiration, or pneumonias.^{121–123} Thus, many institutions have increased their GRV thresholds for stopping enteral feedings up to 500cc, as per current guidelines.¹¹³

Importantly, a recent RCT investigated the effect of not monitoring GRVs at all. In this non-inferiority study, 452 mechanically ventilated adults receiving EN within 36 hours of initiation of ventilation were randomized to either undergo no GRV monitoring or to undergo GRV monitoring every 6 hours with adjustment in the EN delivery rate if GRVs exceeded 250cc.¹²⁴ Patients whose GRVs were not being monitored did experience more vomiting. However, rates of ventilator-associated pneumonia were similar between the non-monitored and monitored group (16.7% vs 15.8%, difference 0.9%, 90% CI –4.8% – 6.7%) and were within the 10% specified non-inferiority margin. Additional clinical outcomes including infectious complications, duration of mechanical ventilation, ICU and hospital lengths of stay, and mortality were also similar between the two groups. These new data should prompt clinicians and institutions to consider changing practice to no routinely monitoring GRVs.

SUPPLEMENTING CALORIES WITH PARENTERAL NUTRITION

Practices with using PN in critically ill patients differ greatly between North America and Europe. European guidelines suggest that parental nutrition should be started within the first two days of critical illness in patients who cannot be adequately fed enterally, while American guidelines recommend against using PN unless there is an absolute contraindication to EN.^{113,125} To investigate this controversy, a group of European investigators randomized 4640 critically ill adults to receive PN initiated early (within the first 48 hours of ICU admission) or late (not until day 8).¹²⁶ All patients received early EN per protocol. Approximately 22% of patients were admitted with sepsis, and slightly more than 41% of patients were emergency admissions. Mortality at 90 days was similar in both groups (11.2% in both, $p=1.00$), and functional status was not different between the groups at discharge. ICU length of stay was shorter in the late-initiation group than in the early-initiation group (3 days [IQR 2–7] vs. 4 days [IQR 2–9], $p=0.02$). Patients in the late-initiation group also had fewer new infections, shorter durations of mechanical ventilation and renal replacement therapy, and a reduction in overall health care costs.

Subsequently, the Australia New Zealand Intensive Care Society Clinical Trials Group investigated the use of PN in patients with contraindications to EN.¹²⁷ In this RCT, 1372 patients with short term relative contraindications to EN were randomized to receive early

PN or standard care. In the standard care group, time to EN or PN was a mean of 2.8 days, while participants in the early PN group because receiving their PN an average of 44 minutes after randomization. In this study, 65% of participants were surgical patients. Only approximately 15% were admitted with either sepsis or a primary respiratory diagnosis, and the proportion of patients with ARDS in this study is not clear. There was no difference in 60-day mortality between the groups (21.5% of early PN vs 22.8% of standard care participants, $p=0.60$). Patients receiving early PN did have an average of $\frac{1}{2}$ fewer days of mechanical ventilation (7.73 vs. 7.26 days, $p=0.01$), but their ICU and hospital lengths of stay were not different than patients receiving standard care. Taken together, these two recent large RCTs, although not restricted to patients with ARDS, indicate that there is likely no benefit in supplementing with parenteral nutrition early in the ICU course to meet caloric goals in a general ICU population that included surgical patients, nor is there a clear benefit to initiating PN early in patients who have short-term relative contraindications to receiving EN. It is important to note that these results are not generalizable to malnourished patients, and current guidelines recommend the consideration of early PN in patients who are unable to receive EN and who are malnourished.¹¹³

PROVISION OF MACRONUTRIENTS AND MICRONUTRIENTS IN PATIENTS WITH ARDS

There are few data available to inform the macronutrient composition of enteral feedings. In general, guidelines suggest critically ill patients should receive an amount of protein daily between 1.5 and 2.0g/kg of ideal body weight. The use of whole protein, or polymeric, formulas is recommended because there are insufficient data to support the routine use of peptide-based formulas in most patients.¹¹³ In most enteral formulas, approximately 25–30% of calories are from fat. Similar to protein, there is insufficient evidence in the literature to support the routine use of high-fat or low-fat enteral formulas.

Several individual micronutrients have been examined over the past decade for their potential benefit in patients with ARDS and in critically ill patients in general.

- Recent data suggest that glutamine, antioxidants, and omega-3 fatty acids are not beneficial in critically ill patients

Glutamine—Glutamine is a ubiquitous amino acid that plays a large role in protein synthesis, and literature has suggested that it may be beneficial in terms of maintaining integrity of the GI lumen. A 2002 systematic review of glutamine supplementation in critically ill patients suggested that it was associated with a reduction in mortality and infectious complications, and that these effects were generally limited to parenteral higher dose glutamine.¹²⁸ While a concentrated dipeptide formulation of intravenous glutamine is available outside of North America and is commonly administered, intravenous glutamine is only available in a formulation in Canada and the United States that has limited solubility and requires excess fluid administration.

In contradiction, a recent blinded 2-by-2 factorialized trial glutamine and antioxidants suggests that supplemental glutamine may be harmful in critically ill patients with organ failure.¹²⁹ In this RCT, 1223 critically ill adults who were mechanically ventilated with at least two organ failures were randomized to receive enteral and parenteral glutamine or

placebo (and were also randomized to receive enteral and parental antioxidants or placebo, discussed below). Approximately 30% of the participants were admitted with a respiratory disorder, and another 30% had sepsis. Mortality at 28 days among those who received glutamine was 32.4% versus 27.2% among those receiving placebo ($p=0.05$), and mortality at 6 months was also greater in the glutamine group. Additionally, glutamine had no effect on infectious complications or rates of organ failure. Although this study was not specifically conducted in patients with ARDS, these recent data indicate that glutamine should not be administered to mechanically ventilated patients with more than one organ failure.

Antioxidants—As oxidative stress plays a prominent role in critical illness and may contribute to worsening systemic inflammation and organ failure, it has been hypothesized that supplementation with antioxidants may improve clinical outcomes. Over 20 trials have investigated antioxidants and minerals in critically ill patients, including various combinations of selenium, zinc, copper, manganese, β -carotene, and vitamins C and E. When the results of these studies were meta-analyzed, antioxidants were associated with a reduction in mortality (risk ratio (RR) = 0.82, 95% CI 0.72–0.93, $p=0.002$), as well as reduction in duration of mechanical ventilation (0.67 fewer days, 95% CI –1.22 to –0.13, $p=0.02$) and a trend towards a reduction in infections (RR= 0.88, 95% CI 0.76 to 1.02, $P = 0.08$).¹³⁰

Subsequent to this meta-analysis in 2013, the above large 2-by-2 factorialized trial of glutamine and antioxidants was published.¹²⁹ The 1223 mechanically ventilated critically ill adults with more than one organ failure were randomized to receive placebo or to receive both intravenous and enteral selenium, as well as enteral zinc, β -carotene, and vitamins C and E. Mortality at 28 days was not different between the antioxidant and control groups (30.8% vs. 28.8%, $p=0.48$). Secondary outcomes including hospital mortality, 6-month mortality, hospital length of stay, ICU length of stay, organ failure, and infectious complications were also not different between the two groups. Again, although this large RCT was not conducted specifically in patients with ARDS, this study population was similar to ARDS patients in that they were all mechanically ventilated with more than one organ failure. The lack of benefit with combined antioxidant supplementation indicates that there is a limited role for antioxidant delivery at the doses given.

Omega-3 Fatty Acids—Through several mechanisms, including alteration of inflammatory cell membrane phospholipid composition, omega-3 fatty acids can modify eicosanoid inflammatory profiles, and delivery has therefore been investigated as a therapy for ARDS and sepsis. The use of feeding formulas containing omega-3 fatty acids (fish oil) in patients with ARDS and sepsis is currently quite controversial. Three prior trials comparing an enteral feeding formula containing omega-3 fatty acids, borage oil (γ -linolenic acid [GLA]), and antioxidants to placebo found benefit, but the control group in those studies received a high fat feeding formula that is not standard of care.^{131–133} However, two additional recent randomized trials of omega-3 fatty acids found no benefit. The first study was a phase II RCT that investigated enteral liquid fish oil vs saline placebo in 90 patients with ARDS and found no difference in biologic (various systemic and circulating markers of

inflammation and injury) or clinical endpoints.¹³⁴ The second study was a large ARDS Network RCT of a twice daily enteral supplement containing fish oil, GLA, and antioxidants compared with an isocaloric control. This study was stopped early for futility after enrollment of 272 patients. Results demonstrated that participants receiving the omega-3 supplement had fewer ventilator-free days (14.0 vs 17.2; $p=0.02$), ICU-free days (14.0 vs 16.7; $p=0.04$), and organ failure-free days (12.3 vs 15.5; $p=0.02$) than participants in the control group. Additionally, 60-day mortality was greater in the omega-3 group (26.6% vs 16.3%, $p=.054$). Explanations for the contradictory finding between these studies are unclear and may include fat and protein content of the control group supplement as well as potential differences with continuous versus bolus delivery of omega-3 fats. More research is needed in this area to provide definitive recommendations, but given the results of the ARDS Network study that was stopped for futility, there is concern for potential harm with these supplements (Box 2).

CONCLUSIONS: NUTRITION IN ARDS

Over the past several years, much research on nutrition in critical illness and ARDS has been performed. Key questions such as the amount of protein that should be delivered remain unanswered, but important information has been obtained. Aggregated data suggest that patients with ARDS should preferentially receive enteral nutrition, and this should be started early within 48 hours of ICU admission to preserve GI lumen integrity and prevent infectious complications. New research demonstrates that in well-nourished relatively young patients with ARDS, provision of both full calorie or trophic enteral feedings during the first 6 days of the ICU course, followed by full calorie feedings, is reasonable and does not affect long-term outcomes. After patients with shock are resuscitated and hemodynamically stable, they can safely receive enteral nutrition even if they are receiving stable lower doses of vasopressors. Additionally, a recent study found that not monitoring gastric residual volumes in most critically ill patients is safe and does not lead to worse outcomes; thus it is reasonable for clinicians to devise enteral feeding protocols for their ARDS patients that do not involve routine monitoring of GRVs. Two recent international RCTs of parenteral nutrition concluded that it is not beneficial as either a caloric supplement to enteral nutrition or an alternative in patients who have a short-term relative contraindication to enteral nutrition. Finally, additional newly published RCTS have found that glutamine and antioxidants, as well as omega-3 fatty acids, are of no benefit in critically ill patients with at least 2 organ failures and with ARDS, respectively.

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Box 1. Management Recommendations for Obese ARDS Patients

- Low tidal volume (6cc/kg) ventilation based on Ideal Body Weight
- Drug dosing based on appropriate body weight (actual, ideal, lean)
- Semi-recumbent positioning and wean upright (45°)
- Anticipate slow wean from mechanical ventilation
- Proper GI & DVT prophylaxis and skin care

Box 2. Clinical Nutrition in Critically Ill Patients with ARDS

- Enteral nutrition, rather than parenteral nutrition, should be used in the vast majority of ARDS patients and should be started within 48 hours of ICU admission.
- Either full feeding or trophic feeding for the first few days of a patient's ICU stay is reasonable.
- After patients with shock are resuscitated and hemodynamically stable, they can safely receive enteral nutrition even if they are receiving stable lower doses of vasopressors.
- Consideration should be given to not monitor gastric residual volumes in most critically ill patients, as new evidence suggests this is safe and does not lead to worse outcomes.
- In reasonably well-nourished critically ill patients, there is no role for parenteral nutrition either as a caloric supplement to enteral nutrition early during the ICU course or in patients who have a short-term relative contraindication to enteral nutrition. The optimal role of parenteral nutrition in malnourished patients is currently being investigated.
- New data suggest that glutamine, antioxidants, and omega-3 fatty acids may not be beneficial in critically ill patients.

Box 3. Clinical Effects of Obesity on ARDS

- Risk of developing ARDS ↑
- Mortality from ARDS $\Leftrightarrow$ /↓
- Duration of mechanical ventilation ↑
- Length of hospital stay ↑

KEY POINTS

1. Among critically ill patients, obesity may be associated with greater risk of development of ARDS, but is also associated with better survival.
2. Rising body mass index is associated with increased length of mechanical ventilation, ICU stay, and hospital stay.
3. Many elements of the metabolic syndrome have been implicated in the effects of obesity on ARDS risk and outcomes.
4. Enteral nutrition should be used in the vast majority of ARDS patients, and the role for parenteral nutrition is extremely limited.
5. Enteral nutrition should be started early, within 24–48 hours of ICU admission, and either full or trophic feedings for the first few days of a patient's ICU stay are reasonable.
6. Consideration should be given to not monitor gastric residual volumes in most critically ill patients, as new evidence suggests this is safe and does not lead to worse outcomes.

Figure 1.

Effects of obesity on respiratory mechanics in ARDS. Obesity prolongs the duration of mechanical ventilation in ARDS through numerous effects on respiratory compliance and airways resistance. Yet, despite appearing to increase the risk of atelectrauma, the development of ventilator-induced lung injury may be reduced in this setting for unclear reasons.

Figure 2.

Obesity, the metabolic syndrome, and the pathogenesis of ARDS. The paradox of obesity-associated increased risk for the development of ARDS, yet associated improvement in ARDS outcomes is schematically summarized. ↑ represents possible synergistic effects of obesity on ARDS pathogenesis, while ⊥ represents possible inhibitory effects (see text). Adapted with permission from Suratt & Parsons, "Mechanisms of Acute Lung Injury/Acute Respiratory Distress Syndrome," *Clinics in Chest Medicine* 27(4):587, 2006.

Table 1
Summary of Published Studies of Clinical Outcomes in Obese Critically Ill Patients with ARDS

	O'Brien <i>et al.</i> ¹⁷	O'Brien <i>et al.</i> ¹⁰	Morris <i>et al.</i> ¹⁸	Stapleton <i>et al.</i> ^{2,5}	Gong <i>et al.</i> ⁵	Soto <i>et al.</i> ⁶
Participants	807	1488	825	1409	1795	751
Design	Secondary analysis of data from one ARDS Network RCT	Cohort study using Project Impact database	Secondary analysis of prospectively collected data from King County Lung Injury Project	Secondary analysis of data from two ARDS Network RCTs	Retrospective cohort study of patients at risk for ARDS from two Boston hospitals	Retrospective cohort study of ARDS patients from two Boston hospitals
ARDS definition	AECC	Diagnosis codes from database	AECC	AECC	AECC	AECC
Primary Outcome (adjusted analyses)	No difference in 28-day mortality between obese and normal weight patients	Significantly decreased hospital mortality in obese compared with normal weight patients	No difference in hospital mortality between obese and normal weight patients	No difference in 90-day mortality between obese and normal weight patients	Increasing BMI (either as linear or categorical variable) significantly associated with development of ARDS.	Increasing BMI significantly associated with AKI.
Secondary Outcomes (adjusted analyses)	No differences in VFDs, achieving unassisted ventilation, or 180-day mortality between obese and normal weight patients	No difference in ICU LOS, hospital LOS, or discharge location between obese and normal weight patients	Significantly longer DMV, ICU LOS, and hospital LOS in severely obese survivors compared with normal weight patients. Severely obese patients also more likely to be discharged to a rehabilitation or skilled nursing facility than to home.	No significant differences in VFDs or OFFDs between obese and normal weight patients	Increasing BMI associated with longer time from ICU admission to development of ARDS. Among 547 patients who developed ARDS, BMI not associated with 60-day mortality.*	Increasing BMI associated with significantly decreased 60-day mortality.*

AECC=American-European Consensus Conference, AKI=acute kidney injury, ARDS=acute respiratory distress syndrome, BMI=body mass index, ICU=intensive care unit, LOS=length of stay, OFFDs=organ failure free days, RCT=randomized controlled trial, VFDs=ventilator free days.

* Although these two studies presumably included many of the same patients, one found no significant association between BMI and death while the other found that increasing BMI was associated with a significant decrease in death. One explanation may be that the multivariable models used in each study adjusted for different variables.

Table 2**Nutrition in ARDS/Critical Illness: Summary of the Evidence**

Intervention	Evidence
EN vs. PN	In mechanically ventilated critically ill patients, EN is associated with fewer infectious complications but no change in survival.
Early vs. delayed EN	Among mechanically ventilated critically ill patients, early EN compared to delayed nutrient intake is associated with a trend towards mortality reduction and significant reduction in infectious complications, but no change in DMV or ICU LOS. Among 6 studies investigating EN versus no EN or IV fluids alone, trends in reduction of mortality and infectious complications hold.
Caloric prescription of EN	In patients with ARDS, there are no differences in VFDs, OFFDs, mortality, infectious complications, or long-term outcomes between patients receiving full or trophic enteral feeding for the first 6 days of their ICU course.
Supplementation of calories with PN	Among general critically ill patients, early supplemental PN to meet calculated caloric goals does not change mortality or functional status at discharge, but does lead to longer ICU LOS, more infectious complications, longer DMV and renal replacement therapy, and higher costs. Among critically ill patients with a relative short term contraindication to EN, early supplemental PN does not affect mortality, ICU LOS, or hospital LOS.
Glutamine	Controversial, but recent data suggest that glutamine should not be administered at higher doses in mechanically ventilated patients with multiple organ failure (increased 28-day and 6-month mortality).
Antioxidants	In mechanically ventilated critically ill patients, no clear benefit of antioxidants including selenium, as well as enteral zinc, β -carotene, and vitamins C and E.
Omega-3 fatty acids	Controversial, with studies of an enteral feeding formula containing omega-3s demonstrating benefits and studies of bolus enteral fish oil finding no benefit.

ARDS=acute respiratory distress syndrome, EN=enteral nutrition, ICU=intensive care unit, LOS=length of stay, OFFDs=organ failure free days, PN=parenteral nutrition, VFDs=ventilator free days